Nutrigenomics in Regulating the Expression of Genes Related to Type 2 Diabetes Mellitus

Karoline Felisbino1,2,3, Juliano Gomes Granzotti1, Larissa Bello-Santos1 and Izonete Cristina Guiloski1,2,3*

1Centro de Ensino Superior de Maringá (CESUMAR), Curitiba, Brazil, 2Programa de Pós-graduação em Biotecnologia Aplicada à Saúde da Criança e do Adolescente, Faculdades Pequeno Príncipe, Curitiba, Brazil, 3Instituto de Pesquisas Pelé Pequeno Príncipe, Curitiba, Brazil

Nutrigenomics is the study of the gene-nutrient interaction and it indicates that some nutrients, called bioactive compounds, can mold the genetic expression or change the nucleotide chain. Polyphenols are secondary metabolites found in plants that are regularly consumed in functional foods and help prevent or delay the onset of type 2 diabetes mellitus (T2DM) and its complications. This article objected to review studies about the interaction of diet with polyphenols and Mediterranean diet in the expression of human genes related to T2DM. Resveratrol acts as an antioxidant, anti-inflammatory, and increases mitochondrial function. Regular consumption of quercetin resulted in improvement of hypertension and suppression of diabetes-induced vasoconstriction. Genistein also showed positive results in T2DM, such as increased cell mass and improved glucose tolerance and insulin levels. Catechins showed efficiency in inducing genes in triacylglycerol biosynthesis, inhibition of fatty acids and cholesterol, and resulting in their participation in mitigating complications of diabetes. Lastly, curcumin was demonstrated to be a protector of the pancreatic islets against streptozotocin-induced oxidative stress. Growing evidence suggest that bioactive compounds such as polyphenols have an important role in T2DM and the prevention and treatment of its complication, as they cause activation or inhibition of related genes.

Keywords: nutrigenomics, type 2 diabetes mellitus, chronic disease, bioactive compounds, nutrients, gene-nutrient interactions, polyphenols

INTRODUCTION

Diabetes mellitus (DM) is a syndrome of multiple etiologies, characterized mainly by chronic hyperglycemia with dysfunctions related to the metabolism of proteins and lipids. The increase in glucose concentrations in the bloodstream (hyperglycemia) may be associated with the inability to produce, secrete, or fail to absorb insulin, or even with a set of all these abnormalities (Kuzuya et al., 2002).

Among the types of diabetes, type 2 diabetes mellitus (T2DM) represents 90% of cases, and it occurs when the body does not properly use the insulin produced or does not produce the required hormone capable of controlling blood glucose (Holman et al., 2015). Some of the
patients do not present, at the beginning of metabolic alterations, symptoms, such as thirst, increased diuresis, leg pains, and visual alterations, however, these can manifest late, becoming aggravating factors, and when the diagnosis is not made early, the complications generated by the disease can be greater. The treatment usually consists of changes in eating habits, physical exercise, and pharmacological therapy (Zheng et al., 2018).

According to Steemburgo et al. (2009), several chronic diseases, such as T2DM, have their pathogenesis associated with genetic and environmental aspects. Among the latter, the diet has the power to contribute to the incidence and the severity of these pathologies. Nevertheless, the diet can have a modulating action on phenotypes linked to genetic changes, and this action is related to gene and nutrient interaction.

A variety of habits and environmental factors, including food, can influence the expression of genes involved in T2DM which could be beneficial or harmful in relation to disease. Great progress has been made in the study of these interactions after the Human Genome Project and with the emergence of genetic nutrition, a field of nutrition that studies the relationship between genome and eating habits (Billings and Florez, 2010; Cole and Florez, 2020).

In this perspective, genetic nutrition highlights what is most recent in the science of nutrition. The concepts of nutrigenomics and nutrigenetics are related but follow a different approach to the understanding of the association between genes and diet. Nutrigenomics studies the nutrients and food structures capable of acting on the expression of genes, in contrast, nutrigenetics studies the variables of the personal genome in relation to how we respond to foods or compounds consumed in a diet (Mickelson et al., 2019). Polyphenols are among these compounds. They are secondary metabolites produced by plants that are part of the human diet. They have the potential to interact with genetic material and may alter the expression of important genes. In addition, they act as antioxidants, anti-inflammatory agents, and have been studied in the prevention and treatment of type 2 diabetes (Nunes et al., 2018; Li et al., 2019).

Thus, this study reviewed the relationship between polyphenols and gene expression in T2DM identifying major genes and scientific evidence.

**DIABETES MELLITUS**

Diabetes mellitus is a metabolic disorder characterized by persistent hyperglycemia in the bloodstream as a result of the disabled action and/or failure in production of the hormone insulin, which has as function to promote glucose entry into cells (Kuzuya et al., 2002; Holman et al., 2015). When insulin is absent or its function is impaired, cells are unable to absorb glucose, which remains in the bloodstream causing hyperglycemia (Asmat et al., 2016).

There are three main types of diabetes: type 1 diabetes mellitus, type 2 diabetes, and gestational diabetes. T2DM stands out among them by being present in about 90% of cases (Cole and Florez, 2020). T2DM is a multifactorial polygenic disease, which is believed to be a result of interaction between multiple genes and environmental factors (Rheinheimer et al., 2017).

According to Mahler and Adler (1999), the pathophysiology of T2DM includes peripheral resistance to insulin, increased hepatic glucose production, and functional impairment of pancreatic cells. In the initial stage of the disease, a decrease in insulin sensitivity known as insulin resistance is observed and, to compensate, pancreatic cells increase insulin secretion resulting in a state of hyperinsulinemia. As the disease progresses, these cells lose the ability to secrete large amounts of insulin to maintain balance and the individual develops a deficiency of this hormone (Asmat et al., 2016; American Diabetes Association, 2020). The main characteristic of T2DM is the development and persistence of hyperglycemia, which occurs in conjunction with hyperglucagonemia and increased hepatic glucose production (García-Chapa et al., 2017; Furmli et al., 2018). Multiple metabolic disorders, such as impaired lipid and lipoprotein metabolism, oxidative stress, subclinical inflammation, vascular endothelial dysfunction, and hypertension accompany T2DM (Spranger et al., 2003; Gadi and Samaha, 2007). These disorders have long-term consequences, such as micro and macrovascular complications, neuropathy, retinopathy, nephropathy, and therefore increased mortality rate (Lloyd et al., 2001; Constantino et al., 2013).

**OXIDATIVE STRESS AND DIABETES**

Free radicals are highly reactive molecules that contain oxygen (or nitrogen) and are naturally generated in small amounts during metabolic reactions. Oxidative stress is an imbalance that occurs when the production of free radicals exceeds the antioxidant defenses resulting in damage to vital biomolecules to membranes and DNA, proteins, and lipids (Wu and Cederbaum, 2003).

The cellular damage caused by these reactive oxygen species (ROS) is related to the pathological process of diseases such as cancer and T2DM (Dandona et al., 1996). Hyperglycemia in DM induces an increase in oxidative stress, favoring the progression, and the appearance of complications of the disease (Nishikawa et al., 2000; Rajendran et al., 2011). The reduction of oxidative stress can happen due to antioxidants, molecules that play an important role against free radicals, acting in order to eliminate them or transform them into less toxic products for the cell (Sies, 1993).

Insulin resistance and pancreatic beta-cell dysfunction are associated with oxidative stress. Diabetic patients showed lower enzyme and antioxidants levels, low markers of oxidative stress, and increased production of ROS, which can contribute to vascular complications in DM (Dandona et al., 1996; Weyer et al., 1999; Kaneto et al., 2007; Jiménez-Osorio et al., 2014).

**NUTRIGENOMICS AND DIETARY FACTORS**

Nutrigenomics studies how nutrients affect gene expression (Marcum, 2020), bringing the perspective of designing and prescribe customized diets according to the individual genetic makeup and expanding strategies for prevention and treatment.
of non-communicable diseases (NCDs), such as obesity, T2DM, inflammatory bowel disease (IBD), and cancer (Fialho et al., 2008). It seeks to observe the variations of genetic polymorphisms, responsible for the absorption, metabolism, and excretion of nutrients and bioactive compounds, acting in conjunction with other sub-areas of studies, including metabolomics, transcriptomics, and proteomics (Dimitrov et al., 2016) that together, allow the discovery of the influences of nutrients in the epigenome or genome and how each individual can be affected (Rist et al., 2006).

The diet alone or in conjunction with other environmental factors may cause epigenetic changes (Fenech et al., 2011), and these changes in the genes have great influences on cellular processes associated with health and disease, hormonal balance, cell signaling, carcinogen metabolism, apoptosis, cell cycle control, changes in energy levels, and angiogenesis (Ferguson, 2006). In addition, offspring can also be affected through embryonic development and long-term health (Trujillo et al., 2006). Therefore, it is necessary to understand the health status and correlate it with the individual nutritional needs (Picó et al., 2019).

Functional foods are then able to interact with the genome, being defined as foods that contain physiologically active components that perform a beneficial function to health in addition to the basic nutritional function (Henry, 2010). These components are called bioactive compounds that, even when present in small amounts, their frequent intake has the ability to reduce the risk of chronic diseases. It is recommended that these compounds can be obtained in their natural form. As examples of bioactive compounds, we can mention the polyphenols, such as resveratrol, quercetin, curcumin, and genistein (Karazawa and Mohan, 2018).

The genes may change during intrauterine life, when the nutrients and other food compounds can modulate gene expressions or even change the nucleotide sequence and modify the response of the organism in the presence of toxic and infectious compounds, in addition, the inherited individual genetic sequence can also influence diet, leading to the suppression of nutrients and risks for NCDs. The knowledge of these interactions between the genome and food contributes to the promotion of health and reduces the risks for NCDs through personalized diets (Paparo et al., 2014; Raiten and Bremer, 2020).

**POLYPHENOLS AND DIABETES GENES**

The Mediterranean diet, rich in polyphenol and others nutrients, consists of a balanced intake of fruits, vegetables, fish, cereals, and polyunsaturated fats, combined with a reduction in the consumption of meat and dairy products and a moderate intake of alcohol, mainly red wine (Di Daniele et al., 2017). This diet has been working to prevent different metabolic disorders such as cardiovascular disease and T2DM, and has been shown to decrease the incidence of neurodegenerative diseases and cancer (Bach-Faig et al., 2011). The application of the Mediterranean diet resulted in a reduction of the rate of diabetes incidence by 52% (Salas-Salvadó et al., 2011).

Polyphenols can interact with the DNA molecule, RNA, or with proteins involved in the activation cascade, changing number, function, and structure. Generally epigenetic mechanisms, such as methylation, DNA demethylation, and histone modifications, whether by phosphorylation, acetylation, or others, may arise from the interaction between the compounds found in food and the genes involved. These modifications are reproduced in the phenotype that can change the state of health and disease. But it is still very complex, due to genetic variability, interaction complexity, and variation in the mode of action of polyphenols. The classification of polyphenols according to the chemical structure is shown in Figure 1 (Nunes et al., 2018; Papuc et al., 2020). Furthermore, the absorption and metabolism of polyphenols in the human body (stomach, intestine, and liver) may have a different impact on human health, and factors, such as bioavailability, intestinal microbiota, and transport proteins, and the type of polyphenol may affect the bioactivity of the consumed polyphenol (Scalbert et al., 2002; Manach et al., 2004; Hoda et al., 2019).

Polyphenols can interact with the epigenome in different ways, which can alter gene expression, causing inhibition or activation. Curcumin, for example, can cause demethylation and interact with transcription factors; catechins such as epigallocatechin-3 gallate (EGCG) can also reduce the methylation mechanism by inhibiting the DNA methyltransferase enzyme and cause phosphorylation of serine and tyrosine residues of histone proteins. Flavonoids, such as Luteolin and genistein can cause acetylation of histone H3 and cause hypermethylation of genes and cause inhibition, as well as resveratrol and folic acid (Han, 2003; Collins et al., 2007; Berner et al., 2011; Vettermi et al., 2011; Goh et al., 2014; Boyanapalli and Kong, 2015; Li et al., 2015).
GENES RELATED TO TYPE 2 DIABETES MELLITUS

Oxidative stress is associated with T2DM (Jiménez-Osorio et al., 2014), therefore, genes as NFE2 and NFE2L2 with a regulatory role in the expression of antioxidant proteins can be targeted for protection against oxidative stress (Fu et al., 2017). Animal models showed that Nrf2 agonists improved insulin resistance and obesity, and prevented pancreatic beta-cell apoptosis (Zhao et al., 2011; Bhakkilyalakshmi et al., 2014; Matzinger et al., 2018).

The PRKAA2 gene (AMPK) is responsible for preventing the production of glucose, cholesterol, and triglycerides by promoting the oxidation of fatty acids. This gene has a relationship with the SIRT1 gene because its functioning results in the activation of the SIRT1 gene, and this causes an increase in the substrate NAD+. The SIRT1 gene is responsible for deacetylation processes and modulation of several other genes and therefore can control hepatic glucose production, lipid metabolism, and sensitivity and insulin production. It may, for example, regulate the activity of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1) causing its deacetylation, which has the function to suppress the production of ROS and regulate mitochondrial biogenesis. And lastly, it is able to reduce the production of hepatic glucose by deacetylation and activation of adenosine monophosphate-activated protein kinase (AMPK; Price et al., 2012; Rato et al., 2014). Therefore, there is a reciprocal activation between AMPK and SIRT1, which is suspended by hyperglycemia, decreasing the expression of AMPK and consequently decreasing the expression of SIRT1 (Cantó et al., 2009; Clarke et al., 2014; Li et al., 2019). Other genes are related to insulin signaling, activation, and production, such as the PI3KRI, IRS1, FFAR1, HNF4A, and ENPP1 genes. The PI3KRI gene encodes a phosphoinositide-3-kinase regulatory subunit 1 enzyme with direct function in the insulin signaling pathway (Karadogan et al., 2018). The IRS1 gene encodes the insulin receptor substrate-1, which after phosphorylate regulates growth cascades, metabolism, and glucose transporter (Keshavarzi and Golshen, 2019). The FFAR1 gene carries the code for the formation of the Free fatty acid receptor 1 protein (Ffar1). This protein and agonists (substances capable of activating Ffar1) can amplify insulin secretion in pancreatic beta cells and control blood glucose (Kohara et al., 2019). The HNF4A gene acts by maintaining glucose homeostasis (Azizi et al., 2019) as it directly activates the expression of the insulin gene. In addition, SNPs in the promoter region of the HNF4A gene were correlated with predisposition to T2DM (Bartoov-Shifman et al., 2002). Finally, the ENPP1 gene inhibits insulin receptor signaling, which is why it is related to the development of insulin resistance when overexpressed (Bacci et al., 2007; Neamati et al., 2017).

Some genes are more directly related to pancreatic β cells. The IGF2BP2 gene plays an important role in regulating the function of pancreatic cells (Huang et al., 2010) and its deregulation is associated with insulin resistance (Cao et al., 2018). In studies with rats, total ablation of IGF2BP2 results in increased insulin sensitivity and glucose tolerance (Yang et al., 2020). The overexpression of the PARPi gene is associated with tissue damage and destruction of β cells, being a highly relevant factor in endothelial dysfunction in diabetes (Garcia Soriano et al., 2001; Pacher and Szabo, 2005).

Glucose transport and production also stand out as important processes in T2DM. The genes SLC2A1 and SLC2A2, for example, encode proteins that transport glucose into the cells, which reduces blood sugar and prevents disease (Kilpeläinen et al., 2007; Fu et al., 2017). The PCK1 and PCK2 genes encode proteins related to the production of glucose and have increased expression in people with diabetes (Cao et al., 2004). The reduction in the expression of the TCF7L2 gene was associated with an increase in β cell apoptosis (Shu et al., 2008) and an increase in hepatic glucose production and a reduction in insulin secretion (Lyssenko et al., 2007). The overexpression of the G6PC gene was observed in glucose intolerance and hyperinsulinemia (Im et al., 2011). Estrogens can also regulate the transport and control the levels of glucose in the adipose tissue and muscle, for example, so the gene ESRI can also be targeted in the treatment or prevention of T2DM (Barreto-Andrade et al., 2018).

Finally, we can also mention genes related to inflammatory processes and oxidative stress. Hyperglycemia promotes the formation of advanced glycation end-products (AGEs) that induce inflammation and oxidative stress, so polymorphisms in the AGER gene have been associated with the risk of type 2 diabetes (Kang et al., 2012; Lin et al., 2012). In addition, the inhibition of the NFKB1 and NFKB2 genes shows a decrease in the inflammatory process, consequently improving hypertension and suppressing vasoconstriction induced by diabetes (Gautam et al., 2017; Behera et al., 2020). In patients with T2DM, we can also observe an increased expression of the FTO gene, which may be involved in oxidative metabolism, lipogenesis, and oxidative stress (Bravard et al., 2011).

The functions associated with T2DM of the commented genes, in addition to the respective bioactive compounds found in foods that show some type of interaction are described in Table 1.

FUTURE PERSPECTIVES

One way to prevent T2DM is to know the related genes and define the foods that can interact with them in a positive way. The results demonstrate that the active ingredients found in some foods, such as resveratrol, quercetin, genistein, catechins, curcumin, and anthocyanins, interact with DNA and show protective effects in relation to T2DM. These compounds interact with related genes mainly in the control of insulin secretion and signaling, oxidative stress, inflammatory processes, cellular apoptosis, and glucose and lipid metabolism. With that, we can say that the bioactive compounds present in functional foods have established functions in the prevention and treatment of T2DM and its complications. Many of the described genes need further studies to become more important.
| Genes          | Protein                                                                 | Function                                                                 | Related foods                                                                                                    | References                      |
|---------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|---------------------------------|
| NFE2L2/NRF2   | Nuclear factor erythroid 2 like 2                                       | Regulator of the expression of antioxidant proteins.                      | Animals and human cells showed that curcumin is a substance capable of reducing oxidative stress in different target (cardiac, muscle, hepatic, etc.) for mechanism epigenetic, more specifically demethylation, that activating NFE2L2/NRF2 gene and can be used in the prevention and treatment of diabetes. Studies with humans and animals show the consumption of EGCG and curcumin is related to the increase in NFE2. These are substances that can reduce the methylation mechanism of the gene, that is, it acts as an epigenetic compound, capable of activating the gene. EGCG green tea inhibits DNA methyltransferase, as does curcumin, which is also capable of regulating histone changes. Studies with rats show the quercetin is a flavonoid present in a variety of foods, such as red onion, broccoli, and apple, and has anti-inflammatory, antioxidant, and anti-apoptotic properties. This flavonoid acts on glucose homeostasis in skeletal muscle, increasing glucose uptake by stimulating GLUT4 translocation by activating adenosine monophosphate-activated protein kinase (AMPK) and in the liver, also by activating AMPK where it resulted in the suppression of glucose-6-phosphatase reducing hepatic glucose production. Resveratrol has allosteric effect and is an excellent activator of the SIRT gene and has been used as a treatment for diabetes by normalizing hyperglycemia, improving insulin sensitivity, decreasing liver glucose production, and regulating mitochondrial biogenesis and lipid metabolism. However, we find a complexity in relation to the mode of action and effect of this polyphenol and dependent on concentration. Studies with human muscle cells have shown that at high concentrations it can be harmful and inhibit mitochondrial respiration. Reeveratrol has allosteric effect and is an excellent activator of the SIRT gene and has been used as a treatment for diabetes by normalizing hyperglycemia, improving insulin sensitivity, decreasing liver glucose production, and regulating mitochondrial biogenesis and lipid metabolism. However, we find a complexity in relation to the mode of action and effect of this polyphenol and dependent on concentration. Studies with human muscle cells have shown that at high concentrations it can be harmful and inhibit mitochondrial respiration. | Zhao et al., 2011                                                                                     |
| NFE2          | Nuclear factor, Erythroid 2                                             | Regulator of the expression of antioxidant proteins.                      | Studies with rats show the quercetin is a flavonoid present in a variety of foods, such as red onion, broccoli, and apple, and has anti-inflammatory, antioxidant, and anti-apoptotic properties. This flavonoid acts on glucose homeostasis in skeletal muscle, increasing glucose uptake by stimulating GLUT4 translocation by activating adenosine monophosphate-activated protein kinase (AMPK) and in the liver, also by activating AMPK where it resulted in the suppression of glucose-6-phosphatase reducing hepatic glucose production. Resveratrol has allosteric effect and is an excellent activator of the SIRT gene and has been used as a treatment for diabetes by normalizing hyperglycemia, improving insulin sensitivity, decreasing liver glucose production, and regulating mitochondrial biogenesis and lipid metabolism. However, we find a complexity in relation to the mode of action and effect of this polyphenol and dependent on concentration. Studies with human muscle cells have shown that at high concentrations it can be harmful and inhibit mitochondrial respiration. | Boyanapalli and Kong, 2015                                                                      |                                           |
| PRKAA2        | 5'-AMP-activated protein kinase catalytic subunit alpha-2                 | It encodes the protein kinase that is activated by AMP molecules. The general function of this protein is to turn on important metabolic pathways for energy production and turn off the pathways that spend a lot of ATP, controlling the body's need for energy according to the situation. | Reeveratrol has allosteric effect and is an excellent activator of the SIRT gene and has been used as a treatment for diabetes by normalizing hyperglycemia, improving insulin sensitivity, decreasing liver glucose production, and regulating mitochondrial biogenesis and lipid metabolism. However, we find a complexity in relation to the mode of action and effect of this polyphenol and dependent on concentration. Studies with human muscle cells have shown that at high concentrations it can be harmful and inhibit mitochondrial respiration. | Njöveldt et al., 2001                                                                  |
| SIRT1         | NAD-dependent protein deacetylase sirtuin-1                             | It encodes the protein called Sir1, that belongs to the family of proteins that interact with the genetic material causing deacetylation of histones, that is, it is able to inactivate genes by an epigenetic mechanism. | Reeveratrol has allosteric effect and is an excellent activator of the SIRT gene and has been used as a treatment for diabetes by normalizing hyperglycemia, improving insulin sensitivity, decreasing liver glucose production, and regulating mitochondrial biogenesis and lipid metabolism. However, we find a complexity in relation to the mode of action and effect of this polyphenol and dependent on concentration. Studies with human muscle cells have shown that at high concentrations it can be harmful and inhibit mitochondrial respiration. | Cantó et al., 2009                                                                 |
| PI3KR1        | Phosphoinositide-3-kinase regulatory subunit 1                          | It forms a protein involved in insulin signaling, cancer, and cytokines (involved in the immune system), and also in adipocyte maturation. | There are a few scientific articles related to nutrigenomics and the PI3KR1 gene. EGCG at low concentrations does not demonstrate activation of the IRS-1 gene, but it does show to be an inhibitor of gluconeogenesis in isolated hepatocytes. However, polyphenol-rich green tea increased the expression of the IRS1 gene in the muscle of the rat. The polyphenol-rich ethyl acetate fraction isolated from Molineria latifolia improves insulin resistance in experimental diabetic rats through the activation of IRS1/AKT, by altering the phosphorylation of gene-related serine and tyrosine residues. | Howitz et al., 2005                                                                 |
| IRS1          | Insulin receptor substrate 1                                            | Insulin signaling.                                                        | There are a few scientific articles related to nutrigenomics and the PI3KR1 gene. EGCG at low concentrations does not demonstrate activation of the IRS-1 gene, but it does show to be an inhibitor of gluconeogenesis in isolated hepatocytes. However, polyphenol-rich green tea increased the expression of the IRS1 gene in the muscle of the rat. The polyphenol-rich ethyl acetate fraction isolated from Molineria latifolia improves insulin resistance in experimental diabetic rats through the activation of IRS1/AKT, by altering the phosphorylation of gene-related serine and tyrosine residues. | Qi et al., 2011                                                                    |

(Continued)
| Genes      | Protein                                      | Function                                                                                           | Related foods                                                                                                                                                                                                 | References                                       |
|------------|----------------------------------------------|----------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| FFAR1      | Free fatty acid receptor 1                   | Metabolic regulation of insulin secretion and hepatic glucose uptake in vitro.                     | Humans cells demonstrated that the anthocyanins present in purple corn have the possibility of activating the FFAR1 gene, a known marker that, when activated, can contribute to the treatment of type 2 diabetes and its complications. Another article also shows that some polyphenols, such as anthocyanin, can activate the FFAR1 gene in pancreatic Beta cells, and point to antidiabetic potentials for prevention and treatment. | Wagner et al., 2014                              |
|            |                                              |                                                                                                    |                                                                                              | Luna-Vital and De Mejia, 2018                    |
|            |                                              |                                                                                                    |                                                                                              | Papuc et al., 2020                               |
| HNF4A      | Hepatocyte nuclear factor 4 alpha            | Regulator of hepatic gluconeogenesis and insulin secretion.                                       | Luteolin, a flavone present in chamomile, peppers, and celery tea, has a lipid-lowering effect by suppressing HNF4A gene in mouse cells, by epigenetic means, related to histone H3 acetylation. There are no articles related to foods or bioactive compounds in the modulation or control of the expression of the ENPP1 gene. However, it has been observed that zinc deficiency can impair the activities of some ectoenzymes, including ENPP1. Diet with less protein intake showed a relationship with the increase in IGF2BP2. But no studies on polyphenols or Mediterranean diet and changes in the expression of this gene have been reported. It is possible to observe the protection of curcumin in pancreatic islet cells exposed to streptozotocin, the compound can decrease the formation of reactive oxygen species (ROS) and inhibit the activation of the poly ADP-ribose polymerase-1 enzyme, encoded by the PARP1 gene, and can also prevent the reduction of ROS levels of free radical scavenging enzymes. In HUVECs cells, it was observed that flavonoids (rutin, quercetin, and flavone) can inhibit PARP activation and improve diabetes complications. These compounds can interact with transcription factors and regulate gene expression. | Stoffel and Duncan, 1997                         |
|            |                                              |                                                                                                    |                                                                                              | Wang et al., 2000                                |
|            |                                              |                                                                                                    |                                                                                              | Silander et al., 2004                            |
|            |                                              |                                                                                                    |                                                                                              | Li et al., 2015                                  |
| ENPP1      | Ectonucleotide pyrophosphatase/phosphodiesterase 1 | Transmembrane glycoprotein with effect on insulin signaling and glucose metabolism. |                                                                                              | Haie et al., 2012                                |
|            |                                              |                                                                                                    |                                                                                              | Neamati et al., 2017                             |
|            |                                              |                                                                                                    |                                                                                              | Gohari-Lasaki et al., 2020                      |
| IGF2BP2    | Insulin-like growth factor 2 mRNA-binding protein 2 | Regulator of cellular metabolism.                                                                 |                                                                                              | Rao et al., 2016                                 |
|            |                                              |                                                                                                    |                                                                                              | Gokarn et al., 2018                              |
|            |                                              |                                                                                                    |                                                                                              | Hu et al., 2020                                  |
| PARP1      | Poly(ADP-Ribose) polymerase 1                | DNA damage signaling.                                                                               |                                                                                              | Pacher and Szabo, 2005                           |
| SLC2A1     | Solute carrier family 2, facilitated glucose transporter member 1, and solute carrier family 2 member 4 | They encode glucose transporters (GLUT 1 and GLUT 4).                                               | A variety of polyphenols, such as catechins, flavonoids, phenolic acids, and among others, are related to the increase in glucose transporters in animals and human cells. | Hanhineva et al., 2010                           |
| SLC2A4     |                                              |                                                                                                    |                                                                                              | Wang et al., 2015                                |
| PCK1       | Phosphoenolpyruvate carboxykinase 1          |                                                                                                    | The plant Juniperus procera, rich in polyphenols, was able to reduce the expression of the PEPCK gene in diabetic rats, in liver and kidney cells, serving as a treatment for hyperglycemia, with anti-inflammatory and hypoglycemic effects. | Cao et al., 2004                                 |
| PCK2       |                                              |                                                                                                    |                                                                                              | Alkhedaide et al., 2019                          |
| TCF7L2     | Transcription factor 7-like 2                | Wnt signaling (β cell proliferation and secretion of the insulin).                                  | The gene is expressed in adipose tissue and SNPs are already being associated with diabetes risk. A randomized clinical trial with people at high cardiovascular risk shows that Mediterranean diet can reduce the adverse effect of the rs7903146 (TT) polymorphism and reduce fasting blood glucose and lipids, in addition to preventing stroke. | Corella et al., 2013                             |
|            |                                              |                                                                                                    |                                                                                              | Haddad et al., 2017                              |
|            |                                              |                                                                                                    |                                                                                              | Beloso et al., 2018                              |
|            |                                              |                                                                                                    |                                                                                              | Grant, 2019                                     |

(Continued)
TABLE 1 | Continued

| Genes | Protein | Function | Related foods | References |
|-------|---------|----------|---------------|------------|
| G6PC  | Glucose-6-phosphatase catalytic subunit | Liver glucose production during fasting or T2DM. | Ingestion of EGCG is also related to the control of gluconeogenesis by suppressing the expression of the glucose-6-phosphatase gene. Treatment with the extract of the saffron stigma reduced the expression of the G6PC gene in diabetic rats. Studies with quercetin demonstrated that this compound activated AMPK and resulted in the suppression of the gene, decreasing the production of hepatic glucose since AMPK negatively regulates G6PC. In a study with CACO-2 cells, high-concentration folic acid has been shown to cause methylation in the ESR1 gene; zebularine decreased the methylation of the gene; genistein caused hypermethylation of the ESR1 gene promoter; resveratrol increased the expression of ESR1 and EGCG induced ESR1 hypermethylation and a non-significant decrease in the expression of the ESR1 gene. Curcumin may have antioxidant and anti-inflammatory properties, and attenuate oxidative stress induced by AGEs, suppressing the expression of the AGER gene in mouse liver cells and cardiac tissue. It has the ability to interact with transcription factors such as NFκB, which reduces gene transcription. Flavonoids (fisetin, apigenin, quercitin, chrysin, isoquiritigenin, rutin, genistein, and others) have anti-inflammatory, antioxidant, and anti-apoptotic properties. These biocompounds can cause inhibition of NFκB, mostly by reducing phosphorylation of proteins, and thus can improve vascularization in diabetics and reduce the risk of hypertension, which has already been observed in different tissues of humans and animals. | Han, 2003  
Eid et al., 2015  
Al-Daghri et al., 2017  
Motamedrad et al., 2019 |
| ESR1  | Estrogen Receptor 1 | It encodes a transcription factor that responds to the action of estrogen and cancer. | | Wang et al., 2006  
Berner et al., 2011  
Haile et al., 2012 |
| AGER  | Advanced glycosylation end-product specific receptor | Specific recipient of advanced glycation end products. | | Kang et al., 2012  
Lin et al., 2012  
Abdel-Mageid et al., 2018  
Egaha-Gorroho et al., 2020 |
| NFKB1 | Nuclear factor kappa B subunit 1, Nuclear factor kappa B subunit 2 | Transcription factor involved in anti-inflammatory pathways. | | Tribolo et al., 2008  
Mahmoud et al., 2013  
Gautam et al., 2017  
Choy et al., 2019  
Behera et al., 2020 |
| NFKB2 | Alpha-ketoglutarate-dependent dioxygenase | It forms a nuclear protein involved in insulin signaling, ROS production, and adipose tissue development. | | Bravard et al., 2011  
Ortega-Azorín et al., 2012  
Loos and Yeo, 2014  
Yang et al., 2017  
Di Renzo et al., 2018 |

EGCG, epigallocatechin-3 gallate; CACO-2 cells, human colon carcinoma cell line; and HUVECs cells, human umbilical vein endothelial cells.

in the prevention and treatment of T2DM and other diseases, like the IRS1, TCF7L2, IGF2BP2, PI3KR1, PCK1, PCK2, and FTO genes that are related to the etiology or control of the disease but there are not many studies on compounds that can modulate their expression. The PRKAA and SIRT1 genes, on the other hand, are very well-studied and, therefore, their manipulation could be used to benefit patients with T2DM or prevent the disease, since both genes, besides being associated with each other, interfere in the expression of other genes. Most studies only seek to know whether there is a change in the expression level of genes or not, there is a lack of information about the mode of action of these bioactives. Finally, most genes are directly related to insulin or glucose metabolism, but there is a great need to study genes involved in other important metabolic processes, such as inflammation, apoptosis, and oxidative stress, which may be linked to the prevention and treatment of the disease in an indirect way, it is also important to recognize that the genetic variants of each gene may respond differently to the compounds. It is noteworthy that most genes are also associated with other chronic diseases, which could encourage further studies on the subject.
AUTHOR CONTRIBUTIONS

KF, JG, LB-S, and IG contributed to the conception and design and drafted and critically revised the manuscript. All authors gave final approval and contributed to the article and approved the submitted version.

REFERENCES

Abdel-Mageid, A. D., Abou-Salem, M. E. S., Salaam, N. M. H. A., and El-Garhy, H. A. S. (2018). The potential effect of garlic extract and curcumin nanoparticles against complication accompanied with experimentally induced diabetes in rats. *Phytomedicine* 43, 126–134. doi: 10.1016/j.phymed.2018.04.039

Al-Daghri, N. M., Pontremoli, C., Cagliani, R., Forni, D., Alokail, M. S., Al-Attas, O. S., et al. (2017). Susceptibility to type 2 diabetes may be modulated by haplotypes in G6PC2, a target of positive selection. *BMC Evol. Biol.* 17:43. doi: 10.1186/s12862-017-0897-z

Alkhdeida, A., Abdo Nassan, T., Abdous, M. M., Hassan Mohamed, E., Hassan Amer, H., et al. (2019). Hypoglycemic and antioxidant effect of juniperus procera extract on rats with streptozotocin-induced diabetes. *Pathophysiology* 26, 361–368. doi: 10.1016/j.phpath.2019.11.001

American Diabetes Association (2020). Classification and diagnosis of diabetes: standards of medical care in diabetes-2020. *Diabetes Care* 43, S14–S31. doi: 10.2337/dc20-S002

Asmat, U., Abad, K., and Ismail, K. (2016). Diabetes mellitus and oxidative stress—a concise review. *Saudi Pharm. J.* 24, 547–553. doi: 10.1016/j.jsps.2015.03.013

Azizi, S. M., Sarhangi, N., Alshari, M., Abbas, D., Meybodi, H. R. A., and Hasanzad, M. (2019). Association analysis of the HNF4A common genetic variants with type 2 diabetes mellitus risk. *Int. J. Mol. Cell. Med.* 8, 56–62. doi: 10.22088/IJIMCM.BUMS.8.2.56

Bacci, S., De Cosmo, S., Prudente, S., and Trischitta, V. (2007). ENPP1 gene, pancreatic beta-cell apoptosis mediated through Nrf2. *Ann. Nutr. Metab.* 51, 129–139. doi: 10.1159/000321514

Bhakkiyalakshmi, E., Shalini, D., Sekar, T. V., Rajaguru, P., Paulmurugan, R., Berner, C., Aumüller, E., Gnauck, A., Nestelberger, M., Just, A., and Barreto-Andrade, J. N., de Fátima, L. A., Campello, R. S., Guedes, J. A. C., Bacci, S., De Cosmo, S., Prudente, S., and Trischitta, V. (2007). ENPP1 gene, pancreatic beta-cell apoptosis mediated through Nrf2. *Ann. Nutr. Metab.* 51, 129–139. doi: 10.1159/000321514

Boyanapalli, S. S. S., and Kong, A. N. T. (2015). "Curcumin, the king of spices": epigenetic regulatory mechanisms in the prevention of cancer, neurological, and inflammatory diseases. *Curr. Pharmacol. Rep.* 1, 129–139. doi: 10.1007/s40495-015-0018-x

Bravard, A., Lefai, E., Meugniai, E., Pesenti, S., Disse, E., Vuillarmet, J., et al. (2011). FTO is increased in muscle during type 2 diabetes, and its overexpression in myotubes alters insulin signaling, enhances lipogenesis and ROS production, and induces mitochondrial dysfunction. *Diabetes* 60, 258–268. doi: 10.2337/db10-0281

Bryan, H. G., and Lee, J. K. (2015). Cholerella ethanol extract induced phase II enzyme through NFE2L2 (nuclear factor [erythroid-derived]-2-like 2, NRF2) activation and protected ethanol-induced hepatotoxicity. *J. Med. Food* 18, 182–189. doi: 10.1089/jmf.2014.3159

Cantó, C., Gerhart-Hines, Z., Feige, J. N., Lagouge, M., Noriega, L., Milne, J. C., et al. (2009). AMPK regulates energy expenditure by modulating NAD + metabolism and SIRT1 activity. *Nature* 458, 1056–1060. doi: 10.1038/nature07813

Cao, J., Mu, Q., and Huang, H. (2018). The roles of insulin-like growth factor 2 mRNA-binding protein 2 in cancer and cancer stem cells. *Stem Cells Int.* 2018:4217259. doi: 10.1155/2018/4217259

Cao, H., Van Der Veer, E., Ban, M. R., Hanley, A. J. G., Zinnman, B., Harris, S. B., et al. (2004). Promoter polymorphism in pck1 (phosphoenolpyruvate carboxykinase gene) associated with type 2 diabetes mellitus. *J. Clin. Endocrinol. Metab.* 89, 989–903. doi: 10.1210/jc.2003-031361

Cole, B., Lu, Y., Chen, Y., and Cheng, J. (2015). The role of Nrf2 in oxidative stress-induced endothelial injuries. *J. Endocrinol.* 225, R83–R99. doi: 10.1530/JOE-14-0662

Choy, K. W., Murugan, D., Leong, X. F., Abas, R., Alias, A., and Mustafa, M. R. (2019). Flavonoids as natural anti-inflammatory agents targeting nuclear factor-kappa B (NFkB) signaling in cardiovascular diseases: a mini review. *Front. Pharmacol.* 10:1295. doi: 10.3389/fphar.2019.01295

Constantino, N. E., Belayev, D., Lambert, D. W., and Turner, A. J. (2014). Epigenetic regulation of angiotension-converting enzyme 2 (ACE2) by SIRT1 under conditions of cell energy stress. *Clin. Sci.* 126, 507–516. doi: 10.1042/CS20130291

Cole, J. J., and Florez, J. C. (2020). Genetics of diabetes mellitus and diabetes complications. *Nat. Rev. Endocrinol.* 16, 377–390. doi: 10.1038/s41583-020-0278-5

Collins, Q. F., Liu, H. Y., Pi, J., Liu, Z., Quon, M. J., and Cao, W. (2007). Epigallocatechin-3-gallate (EGCG), a green tea polyphenol, suppresses hepatic gluconeogenesis through 5'-AMP-activated protein kinase. *J. Biol. Chem.* 282, 30143–30149. doi: 10.1074/jbc.M702390200

Constino, M. L., Molyneaux, L., Limacher-Gisler, F., Al-Saeed, A., Luo, C., Wu, T., et al. (2013). Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. *Diabetes Care* 36, 3863–3869. doi: 10.2337/dc12-2455

Corella, D., Carrasco, P., Sorlí, J. V., Estruch, R., Rico-Sanz, J., Martínez-González, M. A., et al. (2013). Mediterranean diet reduces the adverse effect of the TCF7L2-r7903146 polymorphism on cardiovascular risk factors and stroke incidence: A randomized controlled trial in a high-cardiovascular-risk population. *Diabetes Care* 36, 3803–3811. doi: 10.2337/db13-0955

Dandona, P., Thusu, K., Cook, S., Snyder, B., Makowski, J., Armstrong, D., et al. (1996). Oxidative damage to DNA in diabetes mellitus. *Lancet* 347, 444–445. doi: 10.1016/S0140-6736(96)90013-6

Di Daniele, N. D., Noce, A., Vidiri, M. F., Moriconi, E., Marrone, G., Annichiarico-Petruzzelli, M., et al. (2017). Impact of Mediterranean diet...
pathways of hyperglycaemic damage. *Nature* 404, 787–790. doi: 10.1038/3508121

Nunes, M. A., Rodrigues, F., Vinha, A. F., Alves, R. C., and Oliveira, M. B. P. (2018). *Nutrigenomics and polyphenols.* Cambridge: Woodhead Publishing, Elsevier Inc.

Ooi, D. J., Adamu, H. A., Imam, M. U., Ithnin, H., and Ismail, M. (2018). Polyphenol-rich ethyl acetate fraction isolated from Melolius latifolia ameliorates insulin resistance in experimental diabetic rats via IRS1/AKT activation. *Biomed. Pharmacother.* 98, 125–133. doi: 10.1016/j.biopha.2017.12.002

Ortega-Azorín, C., Sorlí, J., V., Asensio, E. M., Coltell, O., Martínez-González, M. T., Salas-Salvadó, J., et al. (2012). Associations of the FTO rs9939609 and the M4R rs17782313 polymorphisms with type 2 diabetes are modulated by diet, being higher when adherence to the Mediterranean diet pattern is low. *Cardiovasc. Diabetol.* 11:137. doi: 10.1186/1475-2840-11-137

Pacher, P., and Szabo, C. (2005). Role of poly (ADP-ribose) Polymerase-1 activation in the pathogenesis of diabetic complications. *Antioxid. Redox Signal.* 7, 1568–1580. doi: 10.1089/ars.2005.7.1568

Paparo, L., Di Costanzo, M., Di Scala, C., Cosenza, L., Leone, L., Nocerino, R., et al. (2014). The influence of early life nutrition on epigenetic regulatory mechanisms of the immune system. *Nutrients* 6, 4706–4719. doi: 10.3390/nu6114706

Papuc, C., Goran, G. V., Predescu, C. N., Tudoreanu, L., and Ştefan, G. (2020). Plant polyphenols mechanisms of action on insulin resistance and against the loss of pancreatic beta cells. *Crit. Rev. Food Sci. Nutr.* 1–28. doi: 10.1080/19391630.2019.1685444 [Epub ahead of print]

Parsamanesh, N., Moossavi, M., Bahrami, A., Butlet, A. E., and Saehekar, A. (2018). Therapeutic potential of curcumin in diabetic complications. *Pharmacol. Res.* 136, 181–193. doi: 10.1016/j.phrs.2018.09.012

Picó, C., Serra, F., Rodriguez, A. M., Keijer, J., and Palou, A. (2019). Biomarkers of nutrition and health: new tools for new approaches. *Nutrients* 11:1092. doi: 10.3390/nu11051092

Price, N. L., Gomes, A. P., Ling, A. J. Y., Duarte, F. V., Martin-Montalvo, A., North, B. J., et al. (2012). SIRT1 is required for AMPK activation and the beneficial effects of resveratrol on mitochondrial function. *Cell Metab.* 15, 675–690. doi: 10.1016/j.cmet.2012.04.003

Qi, Q., Bray, G. A., Smith, R. S. H., Hsu, F. B., Sacks, F. M., and Qi, L. (2011). Insulin receptor substrate 1 gene variation modifies insulin resistance response to weight-loss diets in a 2-year randomized trial the preventing overweight using novel dietary strategies (POUNDS LOST) trial. *Circulation* 124, 563–571. doi: 10.1161/CIRCULATIONAHA.111.025767

Raiten, D. J., and Bremer, A. A. (2020). Exploring the nutritional ecology of stunting: new approaches to an old problem. *Nutrients* 12:371. doi: 10.3390/nu12020371

Rajendran, R., Garva, R., Krstic-Demonacos, M., and Demonacos, C. (2011). Sirtuins: molecular traffic lights in the crossroad of oxidative stress, chromatin remodeling, and transcription. *J. Biomed. Biotechnol.* 2011:368276. doi: 10.1155/2011/368276

Rao, P., Wang, H., Fang, H., Gao, Q., Zhang, J., Song, M., et al. (2016). Association between IGF2BP2 polymorphisms and type 2 diabetes mellitus: a case-control study and meta-analysis. *Int. J. Environ. Res. Public Health* 13:574. doi: 10.3390/ijerph13060574

Rato, L., Duarte, A. I., Tomás, G. D., Santos, M. S., Moreira, P. L., Sorroco, S., et al. (2014). Pre-diabetes alters testicular PGC1-α/SIRT3 axis modulating mitochondrial bioenergetics and oxidative stress. *Biochim. Biophys. Acta Bioenerg.* 1837, 335–344. doi: 10.1016/j.bbadis.2013.12.008

Rheinheimer, J., de Souza, B. M., Bauer, A. C., and Crispim, D. (2017). Current role of the NLRP3 inflammasome on obesity and insulin resistance: a systematic review. *Metabolism* 74, 1–9. doi: 10.1016/j.metabol.2017.06.002

Rist, M. J., Wenzel, U., and Daniel, H. (2006). Nutrition and food science go genomic. *Trends Biochem. Sci.* 24, 172–178. doi: 10.1016/j.tibs.2006.02.001

Salas-Salvadó, J., Bulló, M., Babio, N., Martínez-González, M. Á., Ibarrola-Jurado, N., Basora, J., et al. (2011). Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus intervention randomized trial. *Diabetes Care* 34, 14–19. doi: 10.2337/dc10-1288

Scalfert, B., Mor, C., Manach, C., and Rémyéé, C. (2002). Absorption and metabolism of polyphenols in the gut and impact on health. *Biomed. Pharmacother.* 56, 276–282. doi: 10.1016/S0753-3322(02)00205-6
Shu, L., Sauter, N. S., Schultness, F. T., and Matveenko, A. V. (2008). Transcription factor 7-like 2 regulates-cell survival and function in human pancreatic islets. Diabetes 57, 645–653. doi: 10.2337/db07-0847.N.S.S

Sies, H. (1993). Strategies of antioxidant defense. Eur. J. Biochem. 215, 213–219. doi: 10.1111/j.1432-1033.1993.tb18025.x

Silander, K., Mohlke, K. L., Scott, L. J., Peck, E. C., Hollstein, P., Skol, A. D., et al. (2004). Genetic variation near the hepatocyte nuclear factor-αR gene predicts susceptibility to type 2 diabetes. Diabetes 53, 1141–1149. doi: 10.2337/diabetes.53.4.1141

Spranger, J., Kroke, A., Möhlig, M., Hoffmann, K., Bergmann, M. M., Ristov, M., et al. (2003). Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European prospective investigation into cancer and nutrition (EPIC)-Potsdam study. Diabetes 52, 812–817. doi: 10.2337/diabetes.52.3.812

Steemburgo, T., de Azevedo, M. J., and Martínez, J. A. (2009). Gene-nutrient interaction and its association with obesity and diabetes mellitus. Arq. Bras. Endocrinol. Metabol. 53, 497–508. doi: 10.1590/S0004-27302009000500003

Stoffel, M., and Duncan, S. A. (1997). The maturity-onset diabetes of the young (MODY1) transcription factor HNF4α regulates expression of genes required for glucose transport and metabolism. Proc. Natl. Acad. Sci. U. S. A. 94, 13209–13214. doi: 10.1073/pnas.94.24.13209

Tavakoli Faradonbeh, R., Zakerk, M., Karimi Akhormeh, A., Mohammadtaghvaei, N., Jalali, M. T., and Yaghooti, H. (2020). Association of the rs3758391 polymorphism in the SIRT1 gene with diabetic nephropathy from Southwest Iran. Int. J. Diabetes Dev. Ctries. 40, 99–105. doi: 10.1007/s13410-019-00742-1

Thauvin-Robinet, C., Auclair, M., Duplomb, L., Caron-Debarle, M., Avila, M., St-Onge, J., et al. (2013). PIK3R1 mutations cause syndromic insulin resistance with lipoatrophy. Am. J. Hum. Genet. 93, 141–149. doi: 10.1016/j.ajhg.2013.05.019

Tribolo, S., Lodi, F., Connor, C., Suri, S., Wilson, V. G., Taylor, M. A., et al. (2008). Comparative effects of quercetin and its predominant human metabolites on adhesion molecule expression in activated human vascular endothelial cells. Atherosclerosis 197, 50–56. doi: 10.1016/j.atherosclerosis.2007.07.040

Trujillo, E., Davis, C., and Milner, J. (2006). Nutrigenomics, proteomics, and the practice of dietetics. J. Am. Diet. Assoc. 106, 403–413. doi: 10.1016/j.jada.2005.12.002

Turnon, M., Garcia-Mediavilla, M., Sanchez-Campos, S., and Gonzalez-Gallego, J. (2009). Potential of flavonoids as anti-inflammatory agents: modulation of pro-inflammatory gene expression and signal transduction pathways. Curr. Drug Metab. 10, 256–271. doi: 10.2174/13892009097846369

Vetterli, L., Brun, T., Giovannoni, L., Bosco, D., and Maechler, P. (2011). Resveratrol potentiates glucose-stimulated insulin secretion in INS-1E β-cells and human islets through a SIRT1-dependent mechanism. J. Biol. Chem. 286, 6049–6060. doi: 10.1074/jbc.M110.176842

Wagner, R., Staiger, H., Ullrich, S., Stefan, F., Fritsche, A., and Häring, H. U. (2014). Untangling the interplay of genetic and metabolic influences involving TCF7L2 and FFAR1. Mol. Metab. 3, 261–267. doi: 10.1016/j.molmet.2014.01.001

Wang, X., Chen, H., Liu, J., Ouyang, Y., Wang, D., Bao, W., et al. (2015). Association between the NF-E2 related factor 2 gene polymorphism and oxidative stress, anti-oxidative status, and newly-diagnosed type 2 diabetes mellitus in a Chinese population. Int. J. Mol. Sci. 16, 16483–16496. doi: 10.3390/ijms160716483

Wang, J. Y., Grabacka, M., Marcinkiewicz, C., Staniszewska, L., Peruzzi, F., Khalili, K., et al. (2006). Involvement of αβ1 integrin in insulin-like growth factor-1-mediated protection of PC12 neuronal processes from tumor necrosis factor-α-induced injury. J. Neurosci. Res. 83, 7–18. doi: 10.1002/jnr.20712

Wang, H., Maechler, P., Antinozzi, P. A., Hagenfeldt, K. A., and Wollheim, C. B. (2000). Hepatocyte nuclear factor 4α regulates the expression of pancreatic β-cell genes implicated in glucose metabolism and nutrient-induced insulin secretion. J. Biol. Chem. 275, 35953–35959. doi: 10.1074/jbc.M000661200

Weyer, C., Bogards, C., Mott, D. M., and Pratley, R. E. (1999). The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J. Clin. Invest. 104, 787–794. doi: 10.1172/JCI7231

Williams, C. B., Hughes, M. C., Edgett, B. A., Scribbans, T. D., Simpson, C. A., Perry, C. G. R., et al. (2014). An examination of resveratrol’s mechanisms of action in human tissue: impact of a single dose in vivo and dose responses in skeletal muscle ex vivo. PLoS One 9:e102406. doi: 10.1371/journal.pone.0102406

Wu, D., and Cederbaum, A. I. (2003). Alcohol, oxidative stress, and free radical damage. Alcohol Res. Health 26, 278–290. doi: 10.1079/prs200606496

Yacoub, R., Lee, K., and He, J. C. (2014). The role of SIRT1 in diabetic kidney disease. Front. Endocrinol. 5:166. doi: 10.3389/fendo.2014.00166

Yang, M., Gallo-ebert, C., Hayward, M., Liu, W., Mcdonough, V., and Nickels, J. T. (2020). Human insulin growth factor 2 mRNA binding protein 2 increases microRNA 33a/b inhibition of liver ARCA1 expression and alters low-density apolipoprotein levels in mice. Mol. Cell. Biol. 40, e00058–e00020. doi: 10.1128/MCB.00058-20

Yang, Q., Xiao, T., Guo, J., and Su, Z. (2017). Complex relationship between obesity and the fat mass and obesity locus. Int. J. Biol. Sci. 13, 615–629. doi: 10.7150/ijbs.17051

Zhao, S. G., Li, Q., Liu, Z. X., Wang, J. J., Wang, X. X., Qin, M., et al. (2011). Curcumin attenuates insulin resistance in hepatocytes by inducing Nrf2 nuclear translocation. Hepato-Gastroenterology 58, 2106–2111. doi: 10.5754/hge.11219

Zheng, Y., Ley, S. H., and Hu, F. B. (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat. Rev. Endocrinol. 14, 88–98. doi: 10.1038/nrendo.2017.151

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Felisbino, Granzotti, Bello-Santos and Guiloski. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.