Regulation of glucose metabolism by bioactive phytochemicals for the management of type 2 diabetes mellitus.

Regulation of glucose metabolism of natural phytochemicals for the management of type 2 diabetes mellitus

Abstract: Type 2 diabetes mellitus (T2DM) is the most prevalent disease and becoming a serious public health threat worldwide. It is a severe endocrine metabolic disorder which has the ability to induce serious complications in all kinds of organs. Although the mechanisms of anti-diabetics have been described before, we focus here on the cellular and physiological mechanisms on the modulation of insulin and blood glucose. As obesity and inflammation are intimately associated with the development of T2DM, the possible relationships of them were described. We investigated and discussed the effects of gut microbiota on insulin resistance in human clinical trials and the potential mechanisms and roles whereby gut microbiota improve glucose metabolism. Phytochemicals have historically underlied their effects with therapeutic potential on T2DM, and nowadays still represent an important pool for the identification of novel drug leads. The anti-diabetic effects of natural species that are used in medicines or as nutraceuticals were described. The objective of the present study was to make a systematic review on glucose metabolism in T2DM as well as to explore the relationship between glucose metabolism and natural phytochemicals.

Keywords: Type 2 diabetes; metabolic pathways; Gut microbiota; Phytochemicals; New therapies

Abbreviations: T2DM: Type 2 diabetes mellitus; IR: Isulin resistance; BMI: Body mass index; IRS-1: Insulin receptor substrate 1; IRS-2: Insulin receptor substrate 2; PI3K: Phosphatidylinositol 3-kinase; PDK1: Pyruvate dehydrogenase kinase isozyme 1; GSK: Glycogen synthase kinase; GLUT-4: Glucose transporter type 4; MAPK: Mitogen-activated protein kinase; JNK: c-Jun N-terminal kinase; Erk: Extracellular signal–regulated kinases; PIP2: Phosphatidylinositol-4,5-bi sphosphate; PIP3: Phosphatidylinositol-3,4,5-trisphosphate; mTOR: mammalian target of rapamycin; TSC1/TSC2: Tuberous sclerosis complexs 1/2; p70S6k: protein S6 kinase; AMPK: AMP-dependent protein kinase; GSH: Glutathione synthesis; GPTA: Glutamic-pyruvic transminase activity; SGLT2: Sodium-dependent glucose transporters 2; TNF-α: Tumor necrosis factor-α; CRP: C reactive protein; IL-6: Iinterleukin-6; GLP-1: Glucagon-like peptide-1; SCFA: The short-chain fatty acids; SCFAs: The short chain fatty acids; PYY: Peptide YY; GPR 43/41: G-protein coupled receptor 43/41; FFAR 2/3: Free fatty acid receptor 2/3; HDAC 6/9: Histone deacetylase 6/9; LPL: lipoprotein lipase; ChREBP: Carbohydrate response element binding protein; SREBP-1c: Sterol response element binding protein 1c; LPS: Lipopolysaccharide; PAMPs: Pathogen-associated molecular patterns; PGN: Peptidoglycan; PRRs: The pattern-recognition receptors; TLRs: The Toll-like receptors; NLRs: The Nod-like receptors; AEA: Endocannabinoid lipids anandamide; CBR1: Receptors cannabinoid receptors 1; eCB: endocannabinoid; ZO-1: Zonula Occludens-1; IAP: Intestinal alkaline phosphatase; TCM: Traditional Chinese medicine; SAC: S-allylcysteine; Bas: Bile acids; LPS: lipopolysaccharides; MIN6: Murine pancreatic β cell lines.

1. Introduction

Diabetes mellitus is a well-known public health issue, affecting 415 million people, causing around 5 million deaths and accounting for 14.5% of all-cause mortality worldwide in 2015 (International Diabetes Federation, 2015). The World Health Organization reports that the worldwide prevalence of diabetes is expected to increase to 642 million by the year 2040, with many new cases of diabetes occurring in developing countries, especially in Asia. This increase in the prevalence of diabetes will inevitably lead to increases in the prevalence of diabetes related complications such as retinopathy, neuropathy, and cardiovascular diseases. Christian Bommer and colleagues report that the cost of diabetes worldwide was USD 1.31 trillion, or 1.8% of the global gross domestic product in 2015 (Bommer et al., 2017). The global estimation of diabetes expenditures is predicted to increase to USD 490 billion in the next 20 years (Zhang et al., 2010a). Type 2 diabetes mellitus (T2DM), also known as “non-insulin-dependent diabetes”, accounts for 90% of all cases of diabetes and has become an epidemic burden in worldwide. T2DM is the most prevalent disease in many modern societies and is becoming a serious public health threat worldwide. It is a complex metabolic disorder characterized by insulin resistance (IR) and impaired islet β cell function, which together result in an inability to supply sufficient insulin to meet the body's demands and eventual β cell loss. Individuals with T2DM experience difficulty in controlling their blood sugar level, which leads to high blood sugar

level, sugar in the urine, and high blood insulin level.

The prevalence of T2DM in western countries reached an epidemic level and even worse in Asian countries in the past decade (Kong et al., 2013). Notably, Asians with T2DM are especially vulnerable to renal injury when compared to Caucasians (Kong et al., 2013). In Asia, rapid economic development in many countries has driven a great increase in diabetes prevalence in the recent decade. The prevalence of T2DM is rising, with many Asian countries featured in the top 10 countries with the highest numbers of persons with diabetes. Urbanization is linked to reduced physical activity, increased obesity rates, and a dietary shift towards more refined carbohydrates and increased fat intake (Ramachandran et al., 2008; Ning et al., 2009). Worldwide, China and India are the top two countries with the most number of individuals suffer from diabetes, with Indonesia and Japan in seventh and ninth place, respectively (International Diabetes Federation, 2015). The prevalence of diabetes in South East Asia is also expected to increase by 70% in the next 20 years. Risk scores derived in Caucasian populations might not perform well in Asian populations as there are different biological factors involved in the development of diabetes. Compared to Caucasians, the onset of diabetes in Asians occurs at lower Body mass index (BMI) levels and younger ages (Hu, 2011). South Asians also experience early declines in β cell function, as well as with more insulin resistant and a younger age of onset of diabetes onset compared to other ethnic groups (Gujral et al., 2013; DECODE Study Group, 2003). Studies have shown that Asian ethnicities have a 2 to 4-fold risk of developing T2DM compared to Caucasian ethnicity (Sacks et al., 2012; Urquia et al., 2011). The mechanisms for this increased risk are likely a combination of both genetic and environmental factors

(Tutino et al., 2014), including the fact that obesity may have a greater effect on insulin resistance in these populations compared to Caucasians (Retnakaran et al., 2006). More important, genetic factors play a crucial role in the pathogenesis of T2DM in the Asian population. A study reported that Asian Indians are excessively IR compared with Caucasians (Abate and Chandalia, 2001). More recently, an excess maternal transmission of T2DM was identified among Asian Indians (Chaithri et al., 2012). On the other hand, many environmental factors, such as diet, lifestyle and BMI, are also reportedly associated with the risk of T2DM in Indians (Ramachandran et al., 2001), as well as in other Asian populations such as Chinese. The high consumption of white rice especially in East Asian is significantly associated with a higher risk of T2DM. The waist-to-stature ratio is more strongly associated with T2DM than BMI in most Asian populations. The gut microbiota is essential for the development and regulation of the metabolism of the host. The intestinal mucosal surface protects the host from pathogenic invasion, is tightly regulated with regard to its permeability and can influence the systemic energy balance. Consumption of diets high in sugar influences the microbiota composition and leads to an imbalanced microbial population in the gut. It has been hypothesized that the gut microbiota could be part of a mechanistic link between the consumption of unbalanced diets and T2DM.

While the causes of T2DM are still not completely understood, it is generally believed that T2DM results from both genetic and environmental factors. To date, little attention has been focused on glucose metabolism and natural phytochemicals. For this reason, the objective of the present study was to make a systematic review on glucose metabolism in T2DM as well as to explore the relationship among metabolic pathways, gut microbiota,

obesity and inflammation. How dietary and microbial metabolites modulate host glucose metabolism was also described.

2. Mechanisms of anti-diabetics

There are two main pathways for body to adjust the blood glucose, one by insulin enhancement, another by glucose metabolism which is without insulin-dependent. Insulin secretion by β cells of islets plays one of most important role in our body for adjusting blood glucose and essential for insulin-regulated glucose metabolism. Insulin affects the blood glucose by one part of glucose influx, glycogen synthesis, glycolysis, and inhibition of hepatic glucose production; or the other part of cell proliferation, apoptosis, and autophagy (Aikawa et al., 2000; Xing et al., 2015; Kane et al., 2002; Yamaguchi and Otsu, 2012). Moreover, there are some major metabolic pathways which have been researched and reported for explaining the mechanisms of anti-diabetics by insulin (**Fig. 1**).

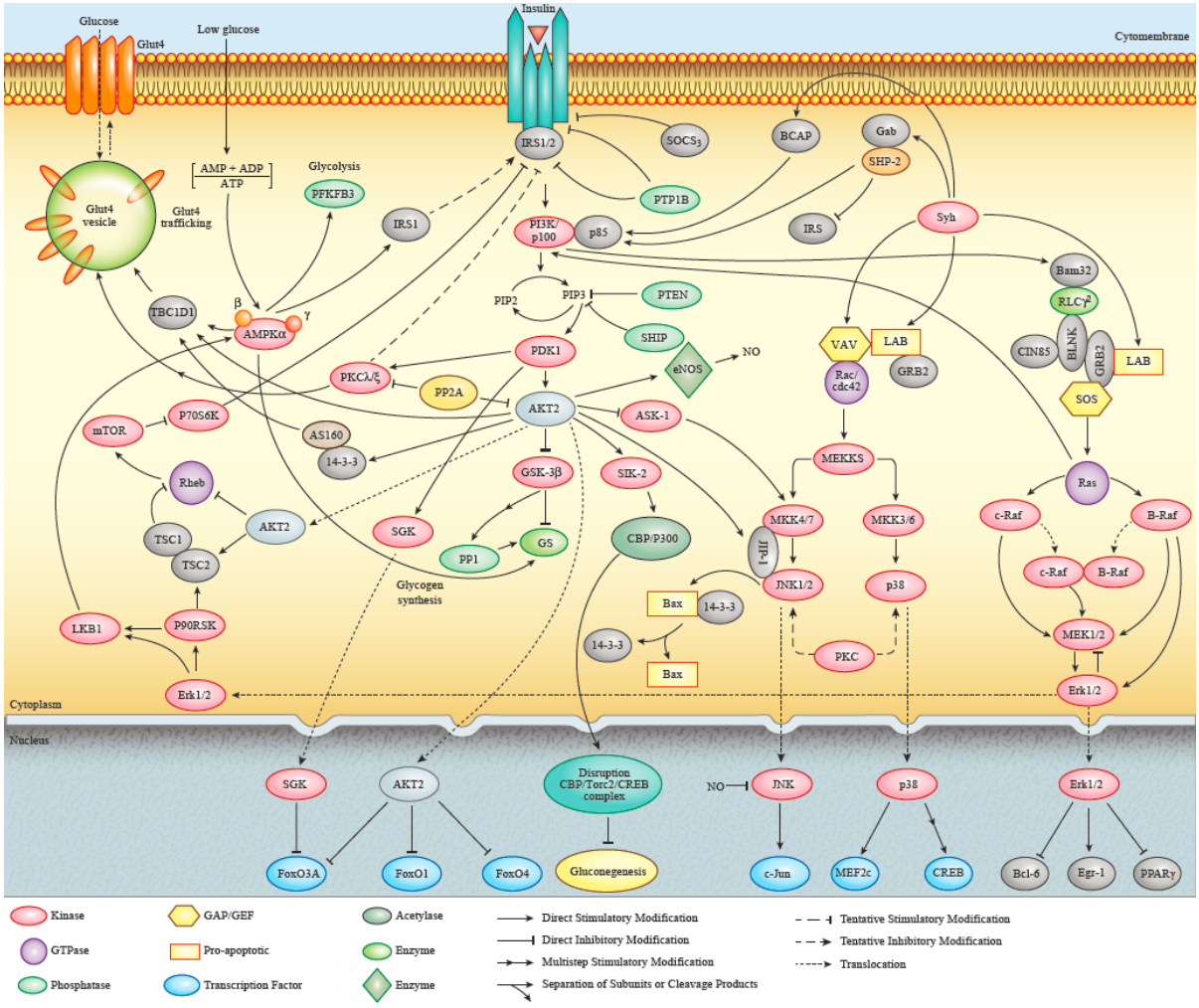

Fig. 1. Main metabolic pathways for body to adjust the blood glucose.

2.1. IRS/PI3K/AKT-GLUT4 pathway activators

Insulin receptor substrate 1 (IRS-1) and IRS-2, the two major substrate proteins generated by phosphorylation of insulin receptor, bind to and activate the phosphatidylinositol 3-kinase (PI3K). The activation of PI3K is a key step of glucose uptake and insulin-induced glucose transport (Tanti et al., 1994). In some extent, the protein p85 sub-unit of PI3K can improve the insulin resistance. The generation of phosphatidylinos-itol 3,4,5-trisphosphate, which can lead to activate of the three known

AKT (protein kinase B) isoforms by pyruvate dehydrogenase kinase, isozyme1 (PDK1), was accompanied by the activation of PI3K. AKT has been regulated by phosphorylation of Thr308 by PDK1 and was a key pleiotropic kinase that affects insulin function on glucose metabolism. It can deactivate glycogen synthase kinase (GSK) and inhibit some pro-apoptotic factors, such as FoxO3A, FoxO1, and FoxO4 in cell nucleus (Paradis and Ruvkun, 1998), and cytoplasm GSK-3β with the development of cell (Mora et al., 2005). Meanwhile, it can also activate glucose transporter type 4 (GLUT-4) by phosphofructokinase for promoting translocation of glucose (Kadowaki et al., 2012; Kahn and Saltiel, 2011; Manning and Cantley, 2007). At the cell surface, GLUT-4 permits the facilitated diffusion of circulating glucose down its concentration gradient via muscle and fat cells. Within cells, glucose is rapidly phosphorylated by glucokinase in the liver and hexokinase in other tissues to form glucose-6-phosphate, which then enters glycolysis or is polymerized into glycogen. Glucose-6-phosphate cannot diffuse back out of cells, which also serves to maintain the concentration gradient for glucose to passively enter cells (Watson et al., 2004). Moreover, GLUT-4 can join the IRS1/2/PI3K/AKT signaling pathway as the insulin-regulated glucose transporter.

2.2. JNK/MAPK/ERK pathway

The mitogen-activated protein kinase (MAPK) signaling pathways, including c-Jun N-terminal kinase (JNK) and extracellular signal–regulated kinases (Erk) pathway, are one of the most importance pathways in models of diabetic and obesity. The JNK signaling has been shown to contribute to a variety of pathological processes associated with diabetes, obesity, heart disease, and cancer (Kane et al., 2002). The molecules JNKs, key members of

MAPK family, are named after their capacities to phosphorylate and activate the Jun family of AP-1 transcription factors (Chang and Karin, 2001; Hibi et al., 1993). Compared with classical MAPK/ERK signaling, JNK pathway is more closely related to glycometabolism than lipid metabolism. The JNK/MAPK pathway comprises a sequential three-tiered kinase cascade. An upstream MAP3K (MEKKs/ASK1) phosphorylates and activates the MAP2K (MKK4, MKK7, MKK3, or MKK6), which then regulate the downstream MAPKs (such as JNKs/p38 MAP kinase) (Chang et al., 2001; Meloche and Pouysségur, 2007). The ASK1 could lead to negative regulation of IRS1 and be deactivated by AKT2. MEKKs are activated by Vav proteins and the member of guanine nucleotide-exchange factors which are GDP/GTP exchange factors for Rho/Rac GTPases. Vav is activated by tyrosine phosphorylation of Syh and SHP-2, which can directly inhibit phosphorylation of IRS. Small G-protein can be distributed into Rho, Rac, and Cdc42 for its function. In other words, the activation of MEKKs is accompanied with activation of cytokines such as Rac and Cdc42.

Advances in genomics and molecular genetics have revealed that the extracellular signal-regulated kinase (ERK) signaling pathway is known as MAPK pathway and a key signaling cascade for modulating multiple cellular functions by phosphorylating and inducing its downstream targets (Chen et al., 2001). ERK/MAPK pathway play an important role on diabetes and malignancies by regulation of cell differentiation, proliferation, growth, apoptosis, gene expression and others (Degen et al., 2012; Mandal et al., 2015; Mebratu and Tesfaigzi, 2009; Zhang and Liu, 2002; Reddy et al., 2003). The SHP-2 and Syh of Erk/MAPK pathway as initial signaling is the same with JNK/MAPK

pathway, which initiates the formation of a 'signalosome' composed of the tyrosine kinases, GRB2/BLNK-related adaptor proteins, signaling enzymes such as PLCγ2, PI3K, and Vav, and small GTPases such as SOS and Ras (Goodnow et al., 2010; Harwood and Batista, 2010). SOS is involved in Ras signaling activation and also acts as a guanine nucleotide exchange factor for Rac to transduce signals from Ras to Rac. In addition, the Ras GTPase subfamily plays a key role in this pathway and activates the MEKK1/2 by phosphorylation of B-Raf or c-Raf. Furthermore, the MEK1/2 can activate ERK kinases (MEK1/2), which inhibits Bcl-6, PPARγ or MEK1/2 and induces Egr-1 DNA-binding activity in the nucleus.

2.3. IRS1/AKT/mTOR-AMPK signaling pathway

IRS1/AKT/mTOR signaling pathway represents a key pathway for genetic variation, diabetes and obesity by cell growth control and autophagy inhibition in cytoplasm (Magnuson et al., 2012; Ganley et al., 2009). PI3K firstly converts phosphatidylinositol-4,5-bi sphosphate (PIP2) into phosphatidylinositol-3,4,5-trisphosphate (PIP3) which activates AKT2 by PDK1 kinase. After that, the activated AKT2 inactivates the conserved serine/threonine protein kinases mTOR (mammalian target of rapamycin) by Rheb-GTPase, which be controlled directly or indirectly by AKT2, or indirectly most likely through the control of tuberous sclerosis complexs (TSC1/TSC2). Finally, mTOR inhibits ribosomal protein S6 kinase (p70S6k) which intensely inhibits phosphorylation of IRS1 (Yin et al., 2017). However, AMP-dependent protein kinase (AMPK) signaling is opposite of IRS1/AKT/mTOR pathway and gets in touch with each other by Erk1/2 in cytoplasm. AMPK has been identified as a critical positive regulator of autophagy, especially as an emerging drug target for T2DM and the metabolic syndrome (Hardie, 2011; Zhang et al.,

2009). AMPK not only directly activates IRS1 and participates in blood glucose metabolism, but also induces autophagy by inhibition of AKT/mTOR pathway. The received signal from cytomembranc stimulated an increase in AMP/ATP ratio and activation of AMPK under low-glucose conditions.

3. Tissues in the regulation of glucose homeostasis

T2DM is a not contagious and severe endocrine metabolic disorder which has the ability to induce serious complications in various organs (Su et al., 2017). In insulin-sensitive organs such as skeletal muscle and adipose tissue, epigenetic modifications might be important in the pathogenesis of T2DM, as the changes alter the profile of genes that control glucose metabolism (**Fig. 2**). T2DM is characterized by the increase in blood glucose levels. Insulin secretion can increase in hepatic glucose output and *de-nove* lipogenesis. T2DM has all inability of tissue cells to utilize secreted insulin against glucose intolerance. (Catalogna et al., 2016; Sharabi et al., 2015; Gugliucci, 2016). It can cause severe secondary complications such as liver dysfunction, kidney failure, heart attack and nerve damage (Manna et al., 2010; Lastra et al., 2010; Hoshino et al., 2016; Jin et al., 2015). The life-threatening T2DM associated complications include long-term damage, dysfunction and failure of the vital organs such as eyes (retinopathy), kidneys (nephropathy), peripheral nerve (neuropathy) and heart vessels (cardiovascular diseases). Pancreas plays a critical role in glucose homeostasis through secreting glucose-lowering hormone insulin and its opponent glucagon (Lovorka et al., 2016). It can decrease blood

glucose levels by reduced triglycerides levels, promoted oxidative stress and improved the function of antioxidant enzymes (Okoli et al., 2010; Ren et al., 2013; Roy et al., 2016). However, impaired insulin secretion by pancreatic β-cells or loss of cell mass and function to insulin biosynthesis can increase β-cells apoptosis and let β-cells proliferation down, which is reflect on higher blood glucose levels (Rutter et al., 2015; Keane and Newsholme, 2014; Mohan et al., 2015). Sustained hyperglycemia can lead to dysregulated glucagon secretion by pancreatic α-cells and elevated glucagon concentration (Song et al., 2014). Liver also plays an important role in T2DM ameliorating via participating in PKC phosphorylation, P13K/AKT and AMPK signaling regulation (Steinbrenner, 2013), GLUT1/4 and glutathione (GSH) synthesis, while decreased glutamic-pyruvic transminase activity (GPTA), mTOR/S6K and oxidative stress (Cordero-Herrera et al., 2015). Other tissue cells are unable to utilize the secreted insulin, thus conduce to high hepatic glucose output, increase in hepatic glucose, glucose production, and *de-nove* lipogenesis (Catalogna et al., 2016; Sharabi et al., 2015; Gugliucci, 2016).

Hyperglycaemia promotes lipid accumulation and glucose reabsorption caused by upregulation of sodium-dependent glucose transporters 2 (SGLT2) receptors in the diabetic kidney (Vallon and Thomson, 2017). Furthermore, it has been proven that proinflammatory cytokines such as MCP-1, TGF-β1 and ICAM1 play a key role in the development of diabetic nephropathy (Du et al., 2015). And the kidney either improved albuminuria or increased AMPK phosphorylation and nephrin/podocin/LXRα□ABCA1 expressions (National Kidney Foundation, 2012). Persistent hyperglycaemia not only promotes the rate of glucose absorption and slows gastric emptying in stomach, but also inhibits

cardioprotection and cardiac function (Maji and Samanta, 2017; Chen et al., 2017). Impaired insulin resistance induced neurotransmitter dysfunction (Hiriart et al., 2014), declined neuroprotection, increased appetite and reduced satiety (João et al., 2016). In addition, insulin inhibits gluconeogenesis and initiates glucose uptake in the muscle and adipose tissues for the maintenance of normal blood glucose levels. Adipose tissue acts as a critical metabolic organ and produces a number of hormones and cytokines such as adiponectin, leptin, AMPK, GLUT4, AKT, TNFα, IL6 and MCP1 (Thea et al., 2015; Zhang et al., 2016). Adiponectin separated from adipose tissue has an insulin-sensitizing and antiatherorgenic activity. However, hyperglycaemia enhanced lipolysis and endothelial dysfunction. Besides, high blood glucose levels inhibit incretin response and lead to glucose absorption and abnormal gut microbiota (Zappas et al., 2017).

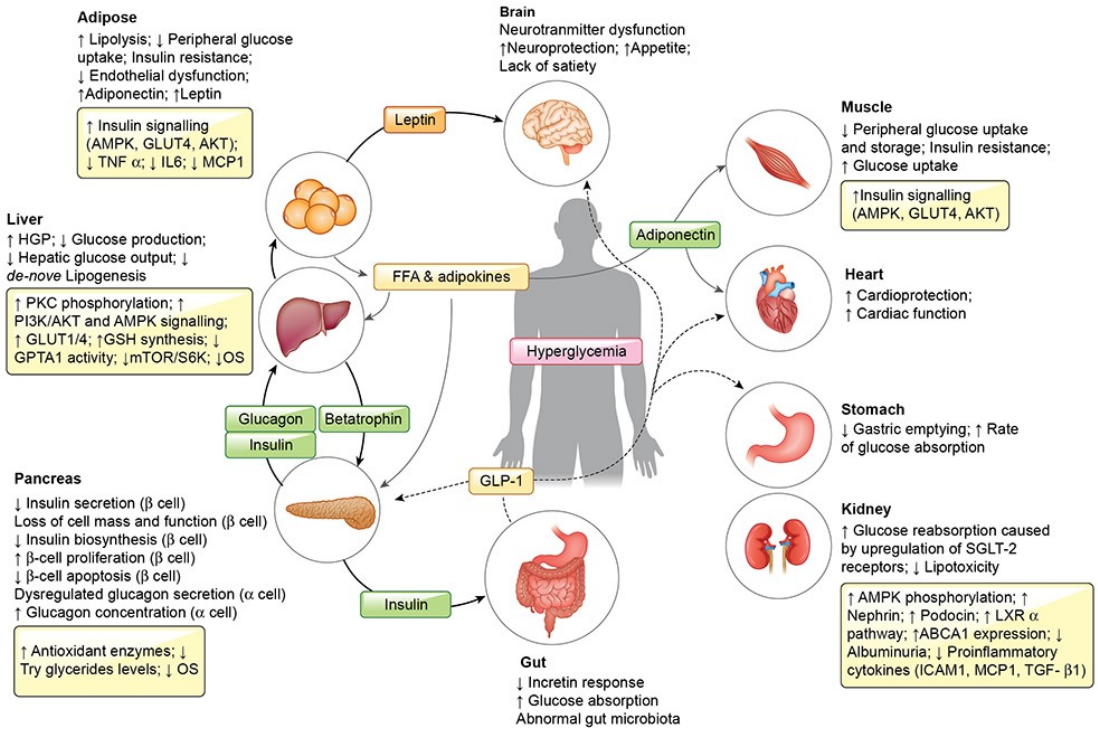

Fig. 2. Tissues in the regulation of glucose homeostasis

4. Type 2 diabetes, obesity, and inflammation

Obesity is strongly associated with an increased risk of T2DM and cardiovascular disease. These conditions are also now recognized as having an inflammatory component (**Fig. 3**). A number of cytokines and inflammatory signaling pathways have been shown to be involved in the development of T2DM, as indicated by increased serum levels of several inflammatory biomarkers, including tumor necrosis factor-α (TNF-α), C reactive protein (CRP), high molecular weight adiponectin, and interleukin (IL)-6. The potential role of inflammation in the complications of obesity is offering further insight into the relationship between T2DM and cardiovascular disease has led to a greater interest on specific therapeutic targeting. Glucagon-like peptide-1 (GLP-1) is a gut hormone, secreted from the intestine in response to meal ingestion, which stimulates insulin secretion and inhibits glucagon release in a dose-dependent fashion (Mazidi et al., 2017). Diabetes is known to have an important inflammatory component. Poor glycaemic control has been found to be positively correlated with levels of inflammatory cytokines such as IL-6 and IL-1β in the circulating blood stream (Calle and Fernandez, 2012). Studies have also shown that the benefit of anti-inflammatory medication as a means of treatment for T2DM (Weisberg et al., 2008). Despite a difference between systemic and neuroinflammation due to the action of the blood brain barrier, there may indeed be some cross-over. Cytokines are now thought to have the ability to cross the blood brain barrier. There is evidence that a hyperglycaemic state increases blood brain barrier permeability (Hawkins et al., 2007). Thus diabetes is relate to a heightened systemic inflammatory response and increased susceptibility of the inflammatory cytokines to enter the central nervous system (Perry et al., 2017).

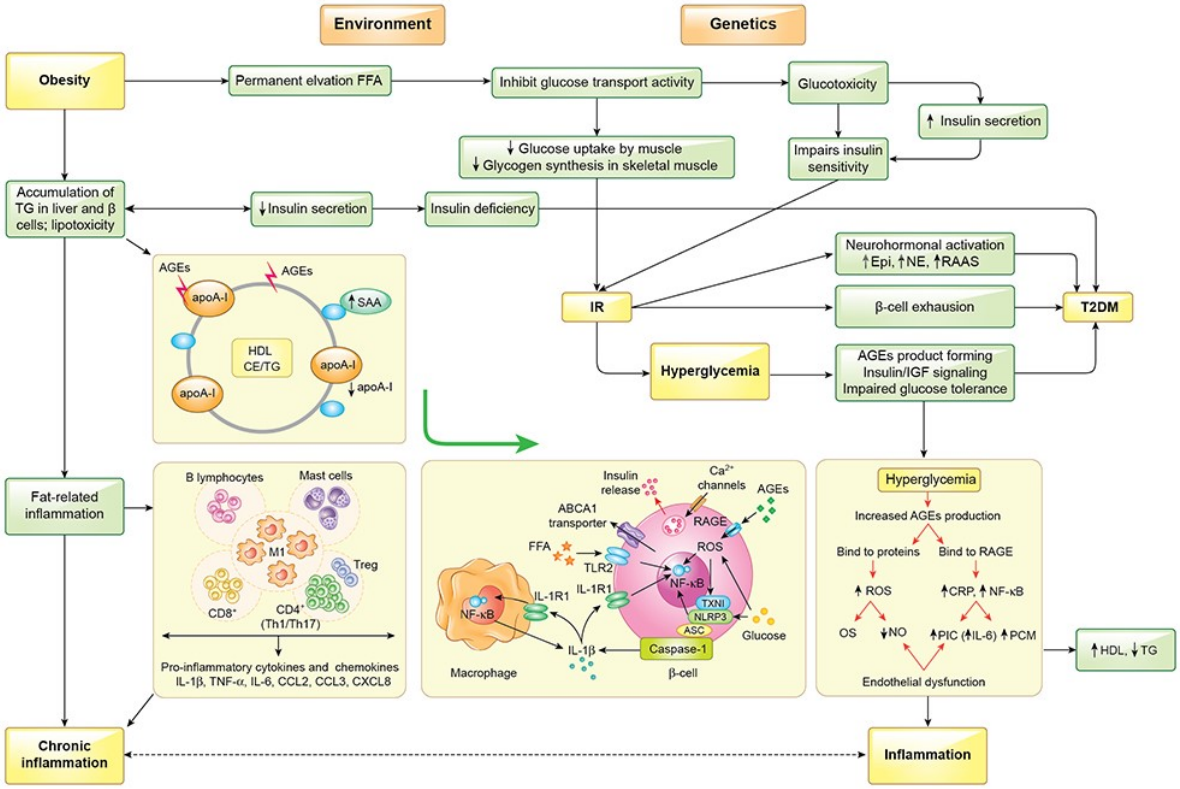

Fig. 3. The relationships among type 2 diabetes, obesity, and inflammation.

5. Effects of gut microbiota and metabolic endotoxemia/bacteremia on diabetes

5.1 Altered gut microbiota composition in diabetes

The endogenous gut microbiota is considered to be a "forgotten organ" participates in whole-body metabolism (O'Hara and Shanahan, 2006). There are approximately 1014 bacteria belonging to more than 1,000 phylotypes in human gut (Whitman et al., 1998). Although the composition of human gut microbiota shows vary greatly between individuals, most of bacteria belong to six well known bacterial divisions/phyla: *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia* (Lozupone et al., 2012; Eckburg et al., 2005), The abundance of *Bacteroidetes* and

Firmicutes comprise the population of 60%-90% of the consortium yet (Neish et al., 2009). Healthy human gut mainly harbors anaerobic bacteria, which of the number is far more than aerobic and facultative anaerobic bacteria (Sommer and Bäckhed, 2013). They are comprised of predominant obligate anaerobes which are belonging to the genera *Bacteroides*, *Eubacterium*, *Clostridium*, *Ruminococcus*, *Peptococcus*, *Peptostreptococcus*, *Bifidobacterium*, and *Fusobacterium.* The following subdominant facultative anaerobes are *Escherichia, Enterobacter*, *Enterococcus*, *Klebsiella*, *Lactobacillus,* and *Proteus* (Guarner and Malagelada, 2003). However, our gut just harbors limited numbers of archaea (mainly *Methanobrevibacter smithii*), eukary (mainly yeasts) and viruses (mainly phage) (Reyes et al., 2010). Several experimental reports have suggested that diet plays a dominant role in forming and changing the bacterial community composition of human gut (Hildebrandt et al., 2009). Moreover, the compositional changes in gut microbiota represent an etiological factor in the development of both insulin resistance and T2DM. Recent studies have shown the gut microbial inhabitants have an influence on the onset of metabolic diseases such as obesity and diabetes. Turnbaugh et al. (2006) confirmed obesity is associated with the shift in relative abundance of the two dominant bacterial phyla, the *Firmicutes* and the *Bacteroidetes*. Specifically, a larger proportion of *Firmicutes* and relatively lower abundance of the phylum *Bacteroidetes* were observed in obese individuals, suggesting that both of them were correlated with energy intake and adiposity (Murphy et al., 2010; Ravussin et al., 2012). At the level of class and below of the microbes, alterations in microbiota composition and diversity have been also involved in obesity-induced IR and T2DM. In contrast to obesity, T2DM-associated microbial dysbiosis is comparatively

modest. The gut microbiome in T2DM was lower levels of short-chain fatty acids (SCFA)-producing bacteria (*Eubacterium rectal*, *Faecalbacterium prausnitzii*, *Roseburia intestinalis* and etc.) and higher levels of known or potential opportunistic pathogens (*Clostridium hathewayi*, *C. ramosum*, and *Eggerthella lenta*) (Qin et al., 2012). And previous studies have shown that functional changes in gut microbiota contribute to the increases in plasma glucose concentrations (Clemente et al., 2015). A moderate degree of gut microbial dysbiosis have appeared on diabetes. Influence of gut microbiota on the development of diabetes is summarized in the present review (**Fig. 4**).

5.2 Gut microbiota and host energy balance and storage

The gut microbiota was reported to participate in the energy energy and general metabolic functions through fermenting undigested carbohydrates, which activate host satiety and decrease food intake (Chambers et al., 2015). Undigested dietary carbohydrates are important sources of energy for human colonic microbiota species, which have the capacity to utilize nearly all of the major plant and host complex glycans, such as two members of the *Bacteroides fragilis* group, *Bacteroides thetaiotaomicron* and *B. ovatus* (Martens et al., 2011). Interestingly, Bifidobacteria are dominant and prevalent members of the (early) microbiota are that they may access glycans in the gut through mutualistic cross-feeding or resource-sharing activities, which is indicative of 'social behavior' among bifidobacterial strains. The short chain fatty acids (SCFAs) are a group of molecules that can both modulate the intestinal barrier and escape the gut to influence systemic health. As the bacterial fermentation products, SCFAs (principally acetate, propionate and butyrate) are readily absorbed by the colonic epithelium (butyrate) and peripheral tissues (acetate and

propionate) (Lin et al., 2012). SCFAs have been also shown to activate the gut hormones glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) through G-protein coupled receptor 43/41 (GPR 43/41) which are also known as free fatty acid receptor 2/3 (FFAR 2/3) (Kaji et al., 2014). Several seminal researches showed that GLP-1 and PYY suppress appetite and energy intake (Lin et al., 2012; Nøhr et al., 2013; Tolhurst et al., 2012). Kjems et al. (2003) reported that GLP-1 led to increased insulin secretion in T2DM patients. The activated GPR 43 inhibits fat accumulation in adipose tissue and promotes the glucose metabolism in other tissues by suppressing insulin signalling in adipocytes (Kimura et al., 2013). The SCFA receptor GPR43 also participates in regulation of inflammatory responses in immune cells (Maslowski et al., 2009). Butyrate and acetate were reported to elevate AMP-activated protein kinase (AMPK) activity (Gao et al., 2009; Sakakibara et al., 2006). AMPK activation enhances cellular energy levels by stimulating glucose transport and fat oxidation as well as inhibiting the synthesis of fatty acid and glycogen (Inoki et al., 2012). Moreover, as a histone deacetylase 6/9 (HDAC 6/9) inhibitor, butyrate was proved to promote FoxP3 expression and both the number and function of FoxP3 (+) Treg cells (Beier et al., 2012; Tao et al., 2007). On the other hand, the gut microbiota promotes fat storage through suppressing the fasting-induced adipose factor (Fiaf) which is a circulating lipoprotein lipase (LPL) inhibitor in the gut epithelium (Bäckhed et al., 2007). The increased LPL activity was associated to the microbiota-induced deposition of triglycerides in adipocytes and adipose tissue (Backhed et al., 2004). The gut microbiota also markedly enhances the hepatic triglycerides synthesis by activating the gene expression of the two key transcriptional factors, carbohydrate response element binding protein (ChREBP) and

sterol response element binding protein 1c (SREBP-1c) (Shen et al., 2013). ChREBP and SREBP-1c are both critical for hepatocyte lipogenesis due to their independent effects on mediating glucose signaling and insulin action in liver respectively, thus improving glucose absorption and insulin levels (Dentin et al., 2004). Hence, the influences of gut microbiota on host energy balance and storage represent a possible pathway linking gut microbiota and obesity and diabetes.

5.3 Metabolic endotoxemia/bacteremia, gut barrier function and diabetes

Gut microbiota-derived metabolic endotoxemia are reported to participate in the onset and progression of inflammation and metabolic complications. Several studies have demonstrated dietary fat facilitates the development of metabolic endotoxemia, such as bacterial lipopolysaccharide (LPS) that is a component of the cell wall of Gram-negative bacteria (Amar et al., 2008). LPS is one of the pathogen-associated molecular patterns (PAMPs), PAMPs also include peptidoglycan (PGN), flagellin and lipoproteins etc. The PAMPs are recognized by the pattern-recognition receptors (PRRs), including the Toll-like receptors (TLRs) and the Nod-like receptors (NLRs). The interaction between the PRRs and the PAMPs induces cytokine and interferon production, which may activate the proinflammatory signaling cascades in peripheral tissues of the body (Icaza-Chávez, 2013). LPS and PGN molecules bind to TLR4 and NOD1 receptors respectively, activation of which by the gut microbiota get involved in diet-induced inflammation and insulin resistance (Cani et al., 2007; Schertzer et al., 2011). TLR5 is expressed on the apical and basolateral surface of intestinal epithelia, which detects bacterial flagellin from both Gram-positive (e.g., *Listeria monocytogenes*) and Gram-negative bacteria (e.g., *Salmonella*

typhimurium) (Hayashi et al., 2001). The activation of TLR5 strongly promoted nuclear factor NF-□B production and driven inflammatory responses (Letran et al., 2011). It is well known that gut mucosal surface is the key site of pathogenic bacteria and metabolic endotoxemia entry into the body. Endocannabinoid lipids anandamide (AEA) and its receptors cannabinoid receptors 1 (CBR1) in endocannabinoid (eCB) system are involved in the regulation of gut barrier function during obesity (Alhouayek and Muccioli, 2012). Muccioli et al. (2010) found the gut microbiota regulates the CB1R expression and AEA content in the intestine. Furthermore, the eCB system regulates epithelial permeability through the distribution and localization of tight-junction proteins, *e.g*. Zonula Occludens-1 (ZO-1) and occluding (Muccioli et al., 2010). Additionally, mucus layer has long been recognized as an important ingredient providing protective gut barrier for the host. Muc2 is the major glycosylated mucin produced in the small and large intestine (Johansson et al., 2008). Normal gut microbiota can stimulate the secretion of Muc2 mucin in the goblet cells to ensure the integrity of the mucous layer structure, and thus maintain gut barrier function (Johansson et al., 2011). Altogether, improvement of gut barrier integrity reduces metabolic endotoxemia and bacteremia, as well as lowers inflammation and glucose intolerance. Recently, intestinal alkaline phosphatase (IAP) is recognized to play a crucial role in LPS detoxification by dephosphorylating and detoxifying the phosphate residues of LPS (Bates et al., 2007). Expression of IAP has been shown to be regulated by the gut microbiota and its activity could be increased through the diet (Lallès et al., 2010). Therefore enhanced IAP activity may contribute to reduction of metabolic endotoxaemia and gut permeability in T2DM and obesity. Future physiological studies are needed to elucidate how the

intestinal branched chain amino acids and other amino acids enter the bloodstream and from which intestinal location they are absorbed. Furthermore, investigations of how dietary changes alone or in combination with microbial or pharmacological interventions may impact the microbiome and, in particular, influence *P. copri* modulation of serum branched chain amino acids levels will open novel avenues to counter the pathogenesis of IR and its linked epidemics of common metabolic and cardiovascular disorders. Gut microbiota are also responsible for the extensive metabolism of phytochemicals such as polyphenols and hence improving the oral bioavailability of phytochemicals and shaping their antidiabetic activities (Eid et al., 2017).

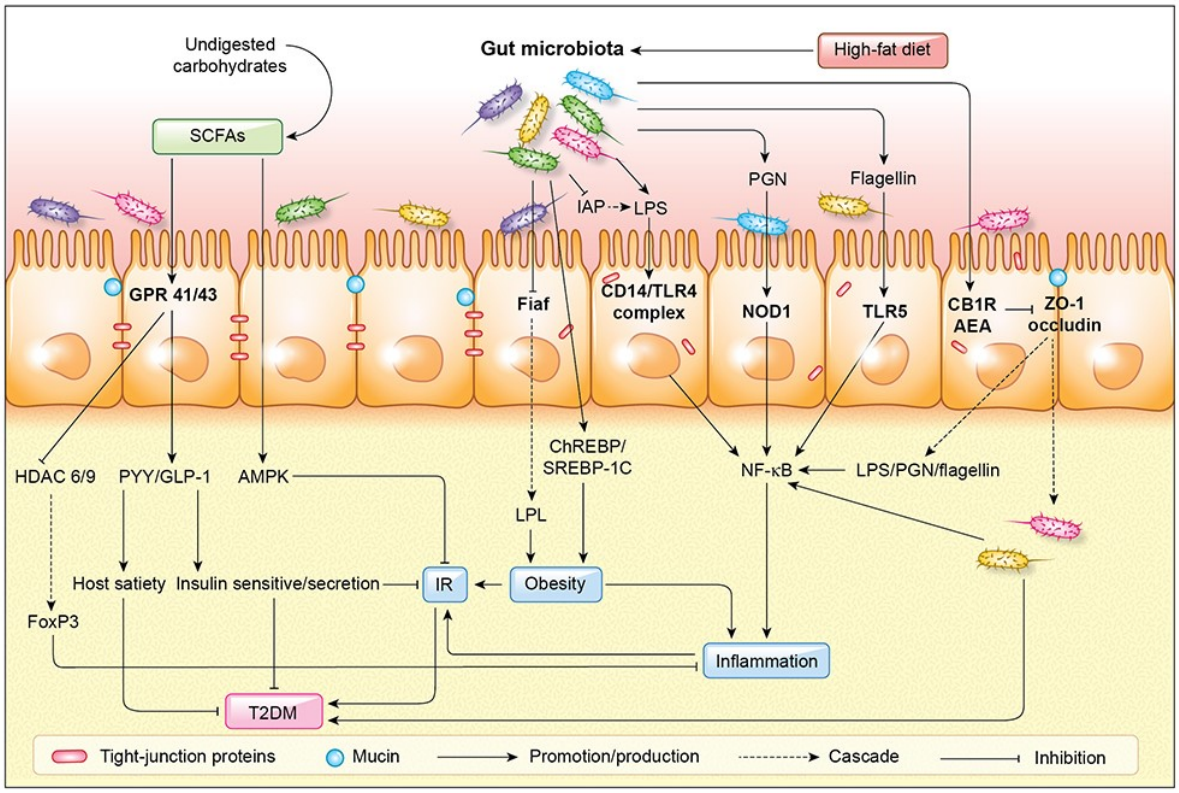

Fig. 4. Effects of gut microbiota and metabolic endotoxemia/bacteremia on diabetes mellitus

Probiotics and/or prebiotics could be a promising approach to improve insulin sensitivity by favourably modifying the composition of the gut microbial community, reducing intestinal endotoxin concentrations and decreasing energy harvest. The anti-diabetic effects of probiotics include reducing pro-inflammatory cytokines via a NF-κB pathway, reduced intestinal permeability, and lowered oxidative stress. SCFAs play a key role in glucose homeostasis through multiple potential mechanisms of action. The potential mechanisms of action could involve insulinotropic and satiety effects mediated by gut hormones, GLP-1 and peptide YY, a β-cell-protective effect by reduced oxidative stress and lowered pro-inflammatory cytokines, anti-lipolytic activities and enhanced insulin sensitivity via GLUT4 through the upregulation of AMPK signalling in tissues (Favaretto et al., 2014). The activation or suppression of the TLRs by microbial signals can dictate the tone of the immune response, and they are implicated in regulation of the energy homeostasis. As modulators of the immune response, the microbiota-derived signals influence functions of distant organs and can change susceptibility to metabolic diseases (Spiljar et al., 2017).

6. Selected Bioactive Natural Products for Diabetes Mellitus

Several plant and mushroom species, including a number of those have been used in traditional Chinese medicine (TCM), have now been shown to have anti-diabetic effects. The future potential of the bioactive natural products used in diabetes treatment will be based on the modification of structures of biologically active compounds (leads), which is a primary requirement for drug development. New approaches for the identification,

characterization, and resupply of natural products are being developed, that may address some of the challenges related to the development of plant-based therapeutics. Resupplying from the original plant species is very unfeasible to meet the huge market demands upon commercialization of a natural product, and alternative resupply approaches are being developed that rely on biotechnological production or chemical synthesis. Over 9000 herbs have known medicinal applications among various cultures and countries. Many plants have been investigated for their beneficial use in different types of diabetes and reported in numerous scientific journals. Some medicinal plants are described below which play a key role in managing diabetes. TCM has a long history and has accumulated considerable clinical experiences, which form a comprehensive and unique medical and cultural system. However, understanding the scientific material basis of TCM herbal formulae at the molecular level and from a systematic perspective for evidence-based TCM remain a considerable challenge.

Scientists have discoveried that plants have great efficacy to produce numerous bioactive molecules dealing with the problem of diabetes mellitus in recent years. These natural products contain large quantities of bioactive compounds including flavonoids, oligo-/polysaccharides, terpenoids, curcumin, xanthones, thiosugar derivatives, tannins, chalcones, phenolic acids, alkaloids and amino acids (Goto et al., 2010). And it is crucial to understand the mechanism behind the biological effects of these compounds for the prevention and treatment of T2DM. Flavonoids are a group of bioactive compounds that usually found in fruits, vegetables, herbs and other plant foods. The routine hyperglycemic period can be responsible for deleterious effects due to glucose toxicity. Flavonoids can

improve the situations in some case. For example, apigenin regulates hyperglycemia by increasing the serum insulin level; anthocyanins prevent the diabetes contribute to the antioxidant property; rutin can improve insulin resistance and increase glucose uptake by enhancing the activities of many enzymes (Raut et al., 2016); and quercetin regulates the diabetes by stimulating insulin secretion, inhibiting aldolase reductase in diabetic patients (Bahman et al., 2014). So, polysaccharides are a class of important compounds that preventing T2DM. *Ganoderma lucidum* polysaccharides decreased plasma insulin concentration and reversed HFD-induced systemic insulin resistance. GLP ameliorated low-grade chronic inflammation, inducing lipolysis in adipose tissues. GLP decreased plasma triglyceride and non-esterified fatty acid outflux by suppressing mRNA expressions of hormone-sensitive lipase, fatty acid binding protein 4, tumor necrosis factor-α, and interleukin-6 in epididymal fat. GLP also regulated composition of gut microbiota implicated in T2DM development (Xu et al., 2017). There are six possible mechanism of polysaccharides to T2DM as follows: (1) elevating plasma insulin, and declining pancreatic glucagon; (2)increasing insulin sensitivity, and improving insulin resistance; (3) scavenging free radicals and lipid peroxidation; (4) increasing hepatic glycogen and inhibiting sugar dysplasia; (5) restricting α-glycosidase enzymes in bowel, and reducing carbohydrates decomposition and absorption (Wang et al., 2017). Studies also found that the mechanism of terpenoids to diabetes through reducing blood glucose level, increasing glycogenesis and decreasing glycogenolysis, inhibiting aldose reductase can also achieve same efficacy. Curcumin is a natural compound that extracted from root of Curcumalonga, it is known to all that curcumin has anti-carcinogenic and anti-oxidant effects (Duvoix et al., 2005;

Shishodia et al., 2005). Its anti-diabetes attribute to inhibiting insulin-regulated GLUT4 translocation and glucose transport (Nabavi et al., 2015). Curcumin by reducing hyperglycemia reported to subside the oxidative stress caused by reactive oxygen species and lipid peroxidation (Raut et al., 2016). Xanthones posses antidiabetic activity due to it have mangiferin and glycoside. The mangiferin have two mechanisms such as decreasing resistance and /or increasing sensitivity, and its glycoside can against several carbohydrate-metabolizing enzymes (Raut et al., 2016). Thiosugar derivatives show strong inhibitory activity against a-glucosidases. Tannins can produce denaturation of proteins and therefore, promoting the nonspecfic inhibition of α-glucosidase, condensed tannins can inhibit α-amylase and higher inhibition can be achieved if the degree of polymerization increases. The antidiabetic of chalcone might attribute to the anti-atherosclerotic activity of 2-hydroxy-4'-methoxychalcone, which has been reported to stimulate PPAR-γ mRNA and protein expression in human aortic smooth muscle cells. The group of chalcone would enhance the sensitivity to insulin. The possible antidiabetic of phenolic acids has been found that they can elevate glucokinase activity and produce the glycogen in the liver. It has been observed that the gallic acid posses antidiabetic activity by inducing glucose uptake by stimulating the GLUT4 translocation. Recent literature data supports the argument that polyphenols can inhibit pancreatic α-amylase or α-glucosidases and this is an important mechanism involved in their hypoglycemic effect. Dietary polyphenols rely on modification either by host digestive enzymes or those derived from the IM for absorption to occur. In the polyphenol-related studies, a large amount of inter-individual variation was observed in the microbial metabolism and absorption of certain polyphenols (Shortt et al.,

2017). S-allylcysteine (SAC) is a sulfur-containing amino acid which can promote the uptake and metabolism of glucose. Furthermore, it can also produce insulin thereby decreasing the blood glucose levels. The antidiabetic mechanism of alkaloids can be described two points: (1) by repairing or proliferation of pancreatic β-cells, stimulating the secretion of insulin, increasing the sensitivity to insulin, decreasing resistance, increasing glycogenesis and inhibiting gluconeogenesis; (2) by decreasing in level of glucogenic enzymes. From the foregoing, it is obvious that plants from nature products have powerful potential to produce many bioactive molecules which posses pharmacological activities especially antidiabetic.

In addition, phytochemicals such as fiber, polyphenols and polysaccharides play a vital role in modulating gut microbiota (phylum *Bacteroidetes*, *Firmicutes* and *Firmicutes*/*Bacteroidetes* ratio, and genus *Akkermansia*, *Bifidobacteria*, *Lactobacillus*, *Bacteroides* and *Prevotella*) through SCFAs, BAs, LPS (Lyu et al., 2017). The administrations of natural phytochemicals lead to increase the abundance of phylum *Bacteroidetes*, and genus *Akkermansia*, *Bifidobacteria*, *Lactobacillus*, *Bacteroides* and *Prevotella*, while reducing phylum *Firmicutes* and *Firmicutes*/*Bacteroidetes* ratio in gut. Natural phytochemicals interact with gut microbiome and alter the microbial metabolites including SCFAs, bile acids (BAs) and lipopolysaccharides (LPS), which are correlated with T2DM.

7. Challenges and Perspectives

Why does T2DM get progressively worse over time, what is the most effective way to slow or prevent progress? The growing prevalence of obesity and T2DM results in an overload of patients at very high short-term cardiovascular risk, and therefore there is a great amount of interest in research into new treatments for T2DM. There is an increasing need for new options to treat diabetes, especially T2DM, at its early stages due to an ineffective control of its development in patients.

7.1 The modification of natural products for medical use

Although the natural products are normally valuable lead compounds, seldom can they be directly used in clinical applications. From the standpoint of drug innovation, it is necessary to modify natural product structures, because the aim in generation of secondary metabolites by organisms is to protect themselves from natural enemies as well as the environment. The final aim of modifying natural products is to developactive compounds into medicines. Structural modifications are necessary. The strategy for structural modification is to increase potency and selectivity, to improve physico-chemical, bio-chemical, and pharmacokinetic properties, to eliminate or reduce adverse effects, to simplify the structural complexity, including removal of redundant atoms and chirality while retaining activities, and to generate patentable compounds. For example, the natural product O-glucoside phlorizin is a well-documented, potent glucosuric agent that was subsequently shown to be a nonselective SGLT inhibitor. Because of its inhibition of SGLT1 with poor metabolic stability due to its susceptibility to β-glucosidase-mediated cleavage, as a lead compound, was modified. Canagliflozin, simplifying structures from phlorizin, entered into clinical trials and was approved by the FDA in 2013 for the

treatment of T2DM (Nomura et al., 2010).

7.2 MicroRNAs as pharmacological targets in diabetes

Recently, a novel class of small non-coding RNAs with approximately 22-nucleotides, termed microRNAs (miRNAs), is found to play a key role as important transcriptional and posttranscriptional inhibitors of gene expression in fine-tuning the target messenger RNAs. It is predicted that over 30% of human genes are regulated by miRNAs which are implicated in the pathogenesis of T2DM and have become an intriguing target for therapeutic intervention. Recent data suggest that miRNAs play a direct role in insulin secretion pancreatic islet development, β cell differentiation, and indirectly control glucose and lipid metabolism and are involved in secondary complications associated with diabetes. MiRNAs are regarded to regulate insulin biosynthesis and secretion in pancreatic β-cells, insulin sensitivity in skeletal muscle and adipose tissue, as well as glucose and lipid metabolism in liver. The first evidence of miRNAs controlling the β cell activities was demonstrated by Poy and his colleagues (Poy et al., 2004). Specific miRNAs play a critical role in controlling β cell activities and the development of diabetic vascular complications. The ubiquity of miRNAs in body fluids and their association with the disease pathogenesis have made them important players for prognosis, diagnosis and management of T2DM. MiR-375 was reported to regulate secretory activities of β cells. Silencing of miR-375 increases glucose-stimulated insulin secretion in murine pancreatic β cell lines (MIN6) and isolated primary β cells. MiR-375 knockout mice exhibited increased pancreatic α-cells, elevated plasma glucagon levels, gluconeogenesis and hepatic glucose output. MiR-7a was recognized to be a negative regulator of adult β cell proliferation by targeting various

components in mTOR signaling pathway (Wang et al., 2013). The specific overexpression of miR-200 in β cell induced β cell apoptosis and promoted severe T2DM under stressed condition by negatively regulating β cell chaperone Dnajc3 or p58IPK and caspase inhibitor Xiap in mice model (Belgardt et al., 2015). Previous findings have reported various miRNA signatures associated with the T2DM, newly diagnosed cases and vascular complications. Although there are multiple numbers of informative studies implicating the role of specific miRNAs in β cell biology, they were mainly carried out with cell lines *in vitro*. Thus, it is of great necessity and urgency to validate of those studies *in vivo* settings no pathophysiological conditions. There is a need to obtain more studies on miRNA expression in human samples highlight the potential roles of miRNAs in T2DM progression. However, pharmacological over-inhibition or overexpression by administration of miRNA mimics or miRNA inhibitors may potentially have off-target effects. More substantial research and standardization of techniques are required to determine the efficacy and feasibility of miRNAs as routinely used diagnostic approaches as well as prognostic markers of T2DM and complications.

7.3 New therapies for type 2 diabetes mellitus

There have been numerous studies focus on new anti-diabetes drugs aimed at improving insulinopenia with fewer side effects than the current insulinotropes (glucokinaseactivators, G protein-coupled receptor ligands, ultra-long acting insulins) and reducing hyperglycaemia (gluconeogenesis inhibitors), and even focus on new drugs with unusual therapeutic pathways, such as the incretinic therapies (GLP-1 analogues), urinary glucose reabsorption inhibitors (sodium-glucose cotrans-porter inhibitors) or inhibitors of other

metabolic pathways with an effect on T2DM and energy metabolism (diacylglycerol acyl-transferase inhibitors, 11-β-HSD1 inhibitors).

8. Conclusions

The growing prevalence of T2DM results in an overload of patients at very high short-term cardiovascular risk. The co-administration of natural products along with conventional medicines is believed to induce a modified bioavailability and important changes of metabolic pathways. Reports show that most of the patients using chronic prescription medications are also associating herbal supplements or vegetal rich diets without understanding the risks. Natural compounds should be avoided as supplements for patients undergoing chemotherapy in order to avoid the risk of decreased availability. Systematic studies are necessary in order to unravel the roles of phytochemicals. This problem is also complementary with the fact that even physicians are not always aware of the risk of interactions. Several products lead to an increase of the drug concentration when administered in short term regimen but may induce an increased metabolism and decreased effect after prolonged intake. It approaches to prevention and treatment involving a combination of factors, such as diet modifications and regular exercise. Dysbiosis of the human gut microbiota impacts the serum metabolome and contributes to insulin resistance. Microbial targets may have the potential to diminish insulin resistance and reduce the incidence of common metabolic and cardiovascular disorders. The objective of the present study was to make a systematic review on glucose metabolism in T2DM as well as to

explore the relationship among metabolic pathways, gut microbiota, obesity and inflammation.

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