

# Can Avicenna Help Manage the Diabetes Epidemic in Central Asia?

Mizhghona Sharofova<sup>1,2,3</sup>, Yusuf Nuraliev<sup>1,2</sup>, Parviz Sukhrovov<sup>2</sup>, Shoista Sagdieva<sup>2,3</sup>, Vyacheslav Dushenkov<sup>4</sup>

<sup>1</sup>Central Research Laboratory, Avicenna Tajik State Medical University, Dushanbe, Tajikistan; <sup>2</sup>Institute of Avicenna's Medicine and Pharmacology, Dushanbe, Tajikistan; <sup>3</sup>Center for Research in Innovative Technologies, the Academy of Sciences of the Republic of Tajikistan, Dushanbe, Tajikistan; <sup>4</sup>Natural Sciences Department, Eugenio María de Hostos Community College of the City University of New York, Bronx, New York, USA

Submitted: July 27, 2017

Revised: September 29, 2017

Accepted: October 5, 2017

## Corresponding Author

Vyacheslav Dushenkov, PhD  
Natural Sciences Department,  
Eugenio María de Hostos  
Community College of the City  
University of New York (CUNY), 500  
Grand Concourse, Bronx, New York  
10451, USA  
Tel: +1-718-518-4444  
E-mail: vdushenkov@hostos.cuny.edu

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. Copyright© 2017 Mongolian National University of Medical Sciences

**Objectives:** The fast-rising rate of diabetes incidents is a growing concern in Central Asian countries. This article reviews the current understanding of type 2 diabetes etiology, progression and treatment options along with opportunities for utilizing Avicenna's legacy in developing novel botanical therapeutics. **Methods:** Analysis of relevant publications, including a variety of Avicenna's work in Arabic, English and Russian. **Results:** With conventional treatment strategy shifting from single-component drugs aimed at one target to multitherapeutic combinations addressing the complex nature of many diseases and conditions, the role of multicomponent botanical preparations may increase. Diabetes mellitus is a serious chronic, progressive disease characterized by hyperglycemia, which is associated with a variety of comorbidities because of considerable damage, dysfunction and failure of multiple organs developed through the disease's progression. Multidisciplinary collaborative research that encompasses innovative tools could be used for effective development of new comprehensive therapeutic products and treatments based on knowledge of traditional medicine and supported by contemporary scientific validation. **Conclusion:** Comprehensive analysis of Avicenna's 1,000-year-old approach to the treatment of prediabetes and diabetes provides valuable directions in the search for plant-based treatments. Botanical therapeutics may provide relatively inexpensive and safe methods for diabetes treatment.

**Keywords:** Diabetes Mellitus, Ethnopharmacology, Traditional Medicine, Medicinal Plants, Metabolic Acidosis, Ibn Sina

## Introduction

Pancreatic  $\beta$ -cell dysfunction and insulin resistance in target organs are the major characteristics of type 2 diabetes mellitus (T2DM), the disease that causes profound psychological and physical distress in patients and puts an enormous burden

on health-care systems. Recent advances in understanding comprehensive molecular and physiological mechanism of glucose metabolism regulations and insulin resistance causalities opened new opportunities in search for anti-diabetic therapeutics and life-style modifications. With conventional treatment strategy shifting from single-component drugs aimed

at one target to multitherapeutic combinations addressing the complex nature of many diseases and conditions, the role of multicomponent botanical preparations may increase. The in-depth analysis of Avicenna's approach to diabetes treatment in combination with contemporary drug development methodology leads to streamlining botanical therapeutics development. Novel botanical therapeutics are essential for reducing the disease burden and prevention.

Central Asia is a vast geographic region with a rich history whose countries are closely related through its nomadic peoples, e.g., the Silk Road, and the Mongol and Russian Empire [1]. Abu 'Ali al-Husayn Ibn Abdullah Ibn al-Hasan Ibn 'Ali Ibn Sina (980-1037), better known in the western literature as Avicenna, influenced multiple generations of physicians. His evidence-based medicinal methodology, ideas and treatment methods are still very popular in Central Asia and make up the foundation of Unani medicine. There is growing interest in reassessing and conducting a deep analysis of the Avicenna's medical *magnum opus* – "The Canon of Medicine" (al-Qānūn fī al-Tibb) [2-4]. Indeed, acceptance of Avicenna's medicine requires understanding of his medical system, avoiding misunderstandings linked to improper translations or misinterpretations, adopting practices and recognition of the evidence-based medicine practiced millennia ago [2, 4]. "The Canon of Medicine" of Avicenna, originally written in Arabic, is a very well-structured source of many theoretical and practical branches of medieval medicine, and a repository of ideas, many of which remain not completely decrypted and may be relevant to modern medicine [5, 6]. After the translation and publication of "The Canon of Medicine" in Latin, English, Russian, Tajik, Persian, Uzbek and many other languages, this *magnum opus* has reached millions of readers. This encyclopedic work is not easy to comprehend and it is still full of unsolved and not yet deciphered secrets. Translation and interpretation of the medieval Arabic text are substantial problems and require not only exceptional language skills and an understanding of ancient medical practices, but also a broad knowledge of modern science. Unfortunately, English translations did not use the original Arabic text, but they were done from other translations (Latin, Urdu, and Farsi) and failed to capture the spirit of the book [2]. It is also important to emphasize that in 2012 non-communicable diseases including diabetes have been the highest-ranking causes in Central Asian countries in terms of disability-adjusted life years and years

of life lost [1]. In this article, we review current approaches to diabetes treatment and prevention and explore how Avicenna's views may help in managing the modern T2DM epidemic.

## Materials and Methods

This review is based on a thorough analysis of the literature in English, Russian, Arabic, and Tajik. The appropriate searches were conducted in Google Scholar (scholar.google.com), PubMed (www.ncbi.nlm.nih.gov/pubmed), KiberLeninka (cyberleninka.ru), eLIBRARY (elibrary.ru). We also used materials available at the Russian National Library (Moscow, Russia) and Central Agricultural Science Library (Moscow Russia). The Institute of Avicenna's Medicine and Pharmacology (Dushanbe, Tajikistan) and the Institute of Philosophy, Political Science and Human Rights of the Academy of Sciences of the Republic of Tajikistan graciously provided access to the books authored by Avicenna.

## Results

### 1. Diabetes

Diabetes mellitus (DM), often referred to as simply diabetes, is a serious chronic, progressive disease characterized by elevated levels of serum glucose (hyperglycemia) (Figure 1), which is associated with a variety of comorbidities, such as blindness, poor wound healing, erectile dysfunction, kidney failure, heart disease, etc; caused by considerable damage, dysfunction, and failure of multiple organs developed through the disease progression. DM occurs either when pancreatic cells do not produce sufficient amount of insulin, or when the cells of the body do not respond properly to the produced insulin. Globally, DM caused over 1.5 million deaths in 2012 and an estimated 8.5% of the adult population (422 million people) were living with diabetes in 2014 with 30.3 million people or 9.4% in the US in 2015 [7, 8]. Out of three generally recognized DM types (type 1 or "insulin-dependent diabetes," type 2 or "non-insulin-dependent diabetes," and gestational diabetes), type 2 (T2DM) is the most prominent constituting about 90% of all cases. T2DM is a growing healthcare burden primarily due to long-term complications. Acute complications can include diabetic ketoacidosis, nonketotic hyperosmolar coma, or even death. Serious long-term complications include heart disease, stroke, chronic kidney failure, foot ulcers, and damage to the eyes. For

example, among adults in China, diabetes was associated with increased mortality from a range of cardiovascular and non-cardiovascular diseases. The prevalence of diabetes in China has more than quadrupled in recent decades, with an estimated 110 million adults having diabetes in 2010 and 490 million adults estimated to have prediabetes [9]. The Republican Clinical Endocrinology Center reports 37,691 people officially diagnosed with diabetes in Tajikistan in 2016, with disease prevalence for different districts ranging from 280 to 678 per 100,000 population. In Mongolia, T2DM is growing problem and a generally poor glycemic control in patients has been reported [10]. It is estimated that worldwide by 2040 one in 10 adults will have diabetes [11].

**2. History of T2DM and the burden of the disease**

Diabetes, in all likelihood, has been recognized as a dangerous metabolic disorder long before it was first mentioned in the Ebers papyrus that provides a comprehensive list of diseases known during the 18th Egyptian dynasty (c. 1630–1350BCE). Descriptions of diabetes have been found in ancient Indian and Chinese medical literature, as well as in the work of ancient Greek and Arab physicians, and in the works of Avicenna (980–1037), who also described complications like sexual dysfunction and gangrene [12-14]. Diabetes was known under different names including the “pissing evil” in the 17th century. The term “diabetes” was probably coined by Apollonius of Memphis around 250 BC from Greek origin meaning “go or pass through.”

**PATHOPHYSIOLOGY OF T2DM**

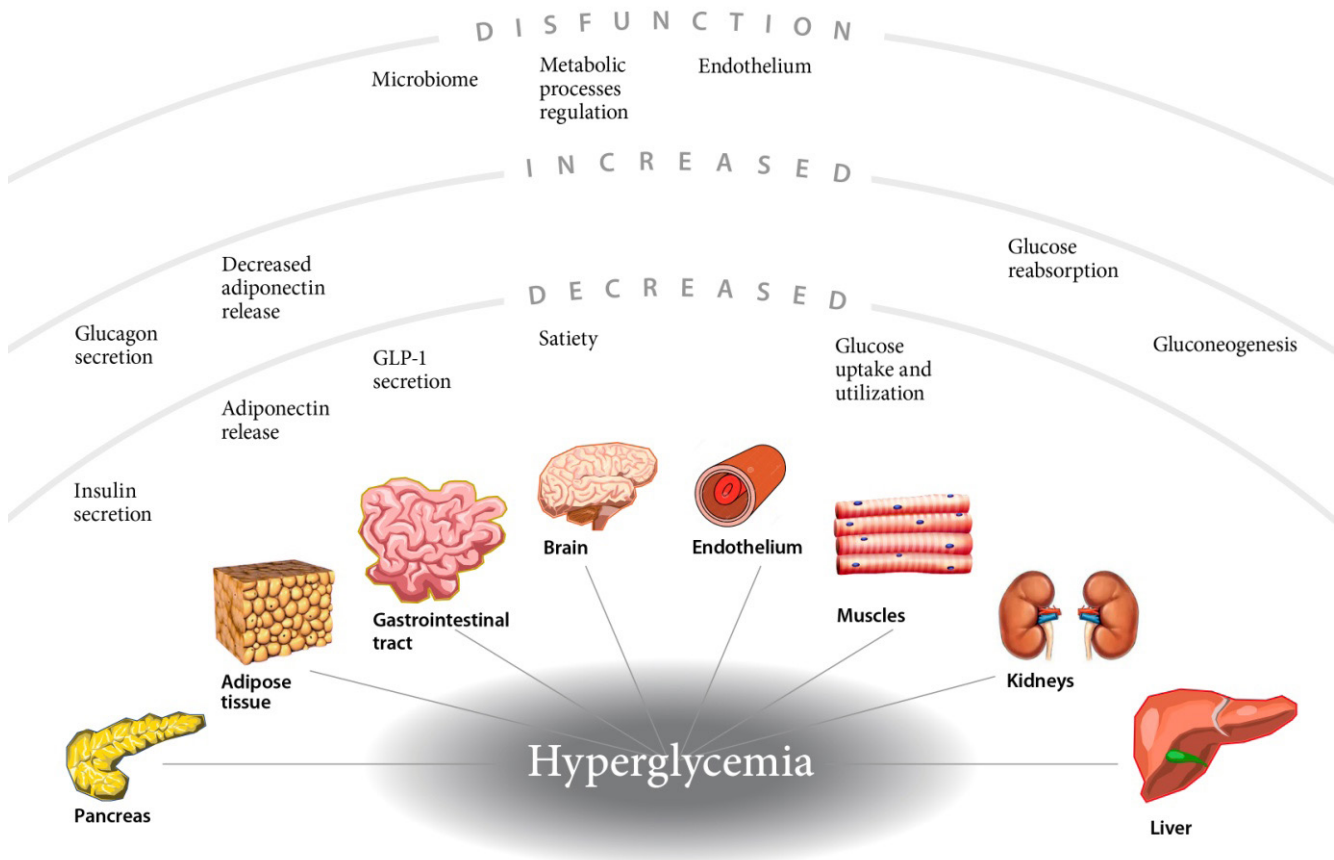


Figure 1. T2DM is a complex multisystem disease comprising numerous metabolic defects that contribute to the development of hyperglycemia.

Diabetes is first recorded in English, in the form “diabete,” in a medical text written around 1425. The English anatomist and physician Thomas Willis (1621-1675) is attributed with adding Latin “mellitus (honey-like, sweet) to Greek “diabetes”—siphon, to pass through—to better reflect one of the major diagnostic parameters of the condition—excessive sugar in urine [14].

T2DM is a complex multisystem disease comprising numerous metabolic defects that contribute to the development of hyperglycemia (Figure 1). Insulin resistance (IR) in the skeletal muscle and liver along with progressive pancreatic  $\beta$ -cell degradation are considered the main causes for the development and progression of hyperglycemia. However, research in the mechanisms of glucose disequilibrium unveiled a very complex network of organ and tissue interaction. Dysfunctions in the gastrointestinal tract, endothelium, adipose tissue, pancreatic alpha cells, brain, and kidneys have been described, and, together with insights into the involvement of liver, muscle, and  $\beta$ -cells produce a robust picture of T2DM pathology (Figure 1). There is a growing understanding of oxidative stress playing an important role in the pathogenesis of IR, dyslipidemia and metabolic syndrome [15]. As pathophysiologic mechanisms and defects continue to be discovered, they offer an expansion of potential targets for treatment of T2DM [16].

The specific courses of T2DM development remain unknown even though associated risk factors and overall pathogenesis have been described at length. IR, decreased sensitivity to circulating insulin, is the defining key pathology that triggers compensatory hyperinsulinemia and when pancreatic  $\beta$ -cell capacity is insufficient to maintain glucose homeostasis, leads to the development of T2DM.  $\beta$ -cell failure, along with IR in muscle and the liver, represents the core pathophysiologic defects in T2DM. A number of pathophysiological abnormalities linked to IR development were added to diabetes pathophysiology to reflect the complex nature of hyperglycemia (Figure 1). Multiple factors are directly linked both to the onset of diabetes and its progression, and are targets for T2DM treatment and prevention. Recent progress in describing the molecular mechanisms of IR significantly improved our understanding of pathways of T2DM onset and progression [17].

### 3. Etiology of T2DM

IR is a primary factor in hyperglycemia a key symptom of T2DM. Even though the exact causes for the development of T2DM are still

not very clear, several important risk factors have been identified. A combination of inherited, behavioral and environmental factors leads to metabolic syndrome and eventually to the T2DM onset. Among the key factors are excess body weight, physical inactivity and poor nutrition. Ethnicity, family history of diabetes (genetics), past history of gestational diabetes, birth weight, certain medications, smoking and advancing age also play an important role [18]. The identification of novel biologic predictors for T2DM and IR may help improve risk assessment and unveil causal pathways beyond established genetic and lifestyle-related factors. Recent advances have made large-scale -omics studies possible that have pinpointed several tentative novel biomarkers for T2DM, including branched-chain amino acids and circulating micro RNAs. Molecular mechanisms of IR are being studied at length [19-22]. It has been shown that p53 has the capacity to control the expression of metabolism-related genes that are important regulators of metabolic pathways, including glycolysis, oxidative phosphorylation, fatty acid metabolism and mTOR signaling [23]. Intensive research in biomarkers for IR has suggested several target candidates, including adiponectin, retinol-binding protein-4 (RBP4), chemerin, adipocyte fatty acid-binding protein, fibroblast growth factor (FGF21), fetuin-A, myostatin, interleukin (IL-6), irisin, and ghrelin, all of which may play a significant role in determining insulin sensitivity [24-26]. The elevation in baseline serum uric acid was found to be an independent risk factor for gout, hypertension and both IR and T2DM [27]. Further, a recent meta-analysis demonstrated an association of low-density lipoprotein cholesterol (LDL-C)-lowering genetic variants in or near *Niemann-Pick C1-Like 1 (NPC1L1)* and some other genes with a higher risk of T2DM [28]. In addition, among the Apolipoprotein A-V (APOA5) gene SNPs, the C allele of -1131T>C polymorphism is a risk factor for metabolic syndrome [29]. However, it is not clear yet what could be gained from adding novel circulating biomarkers and genetic markers to traditional T2DM risk factors.

## 4. T2DM as systemic disease

### 4.1. Muscles

In muscles, IR is manifested by impaired glucose uptake following ingestion of a carbohydrate meal and results in postprandial hyperglycemia. The signal transduction cascade from insulin receptors to glucose transporter type 4 (GLUT4), which ultimately is responsible for insulin-stimulated muscle

glucose uptake, is well understood and includes insulin receptor substrate (IRS1) and phosphatidylinositide 3-kinases (PI3K)/Akt signaling pathway [30, 31]. Elements of this cascade are linked to AMP-activated protein kinase (AMPK), glycogen synthase kinase-3 (GSK3), and mammalian target of rapamycin (mTOR) pathways that play an important role in cell energy metabolism [32]. GLUT4 is in the center of glucose uptake by skeletal muscles and T2DM is linked to GLUT4 dysfunction or reduction in GLUT4 gene expression. IR is strongly associated with increased intramyocellular lipid content and inflammation. However, specific molecular mechanisms responsible for IR onset are still obscure. Molecular mechanisms of the IR include a variety of possible pathways interfering with insulin-GLUT4 signal transduction cascade. One of the best studied is a lipid-mediated (e.g., diacylglycerols, fatty acids) the IR [22, 33, 34].

#### 4.2. Liver

The liver plays an essential role in glucose metabolism. In a normal state, the combination of hyperinsulinemia and hyperglycemia maximizes net hepatic glycogen synthesis. In the liver, IR is manifested by an overproduction of glucose during the basal state despite the presence of fasting hyperinsulinemia in response to insulin, following a meal. Insulin is a central regulator of the postprandial transition of hepatic glucose metabolism from glucose production to glucose storage. Hepatic insulin action requires a coordinated relay of intracellular signals and includes both direct and indirect mechanisms [22, 35]. It was demonstrated that diacylglycerol (DAG)-mediated activation of protein kinase C (PKC) $\epsilon$  impairs hepatic insulin signaling, reduces hepatic glycogen synthesis and strongly correlates with increased glucose production [36]. In addition, substrate flux manifested as additional glucose diverted to the liver due to muscle IR, leading to *de novo* lipogenesis and hyperlipidemia and FAs being released in adipose lipolysis in white adipose tissues, further drive hepatic lipid synthesis and activates hepatic gluconeogenesis Acetyl-CoA-mediated activation of pyruvate carboxylase, increasing glucose production [22, 37].

#### 4.3. Pancreas

##### 4.3.1. Pancreatic $\beta$ -cells

IR places a major stress on pancreatic  $\beta$ -cells to enhance their secretion of insulin to offset the reduction in insulin action. Provided  $\beta$ -cells are able to increase their secretion of insulin

sufficiently to counter balance IR, glucose tolerance remains normal. However, gradually, the  $\beta$ -cells begin to fail and initially the postprandial plasma glucose levels and subsequently, the fasting plasma glucose concentration begins to rise, leading to the onset of overt diabetes [38]. Impairments in  $\beta$ -cell mass and in insulin secretion have been reported in numerous studies in patients with T2DM [39]. There is a tight relationship between the mass of pancreatic  $\beta$ -cells and functional insulin secretion. The onset and pace of  $\beta$ -cells failure determine the rate of progression of hyperglycemia. A variable combination of loss of mass and loss of function appears in T2DM [39]. The  $\beta$ -cells mass remains constant during adulthood, indicating that  $\beta$ -cell turnover is limited in humans. Recent studies have suggested that there is an increase in  $\beta$ -cell neogenesis in humans with obesity, pregnancy and impaired glucose tolerance; however, the extent of its contribution to  $\beta$ -cell mass remains unclear [40]. By the time a diagnosis of diabetes is made, the patient has lost over 80% of his/her  $\beta$ -cell function, and it is essential that the physician intervenes aggressively with therapies known to correct pathophysiological disturbances in  $\beta$ -cell function [41].

##### 4.3.2. Pancreatic $\alpha$ -cell.

In T2DM subjects, dysregulation of the pancreatic  $\alpha$ -cell activity, linked to abnormal sensitivity to glucose with less suppression during hyperglycemia, leads to the elevated basal plasma glucagon concentration and in the increased basal rate of hepatic glucose production [41]. Thus, in diabetic subjects with persistent fasting hyperglucagonemia, postprandial hepatic glucose production remains elevated at fasting levels rather than making the rapid postprandial decline typical of nondiabetic subjects. Glucagon excess, rather than insulin deficiency, may be essential for the development of diabetes. Suppressing glucagon action should effectively decrease the long-term complications and metabolic derangements of diabetes, enhancing the quality of life of diabetic individuals [42]. Glucagon is the chief secretory product of  $\alpha$ -cells and has been the principle measure of  $\alpha$ -cell function. Dysregulated glucagon secretion plays an important role in the pathogenesis of T2DM. Glucagon secretion is normally downregulated by high glucose levels, insulin, amylin, somatostatin and glucagon-like peptide 1 (GLP-1) [43]. Physiological effects of glucagon are defined by its hypoglycemic counter regulation and include increased hepatic glucose production, reduction of glucose oxidation and rapid

mobilization of stored glucose for export to the circulation. Also, glucagon mediates the enhanced rates of hepatic lipid oxidation characteristic of fasting, effects that were due to G-protein-coupled glucagon receptor activation of peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ) and p38MAPK signaling to increase the expression of enzymes involved in  $\beta$ -oxidation [44]. Accelerating lipid oxidation provides energy for glucose anabolism. It is well-established that in states of poorly controlled diabetes with severe insulin deficiency or ketoacidosis, plasma glucagon concentrations are extremely high and that failure to suppress fasting levels of glucagon after eating contributes to hyperglycemia [45, 46]. With clinical studies underway, it has become apparent that suppression of glucagon secretion or antagonization of the glucagon receptor constitutes potentially effective treatment strategies for patients with T2DM [43, 47].

#### 4.4. Gastrointestinal tract

The incretin effect refers to a well-established fact that glucose administered orally elicits a significantly greater insulin response compared to an intravenous glucose infusion. The joint action of two insulinotropic intestinal peptides, glucagon-like peptide (GLP-1) and gastric inhibitory polypeptide (GIP), is responsible for the incretin effect and a decrease in blood glucose levels [48]. The gut hormones, GLP-1 and GIP, secreted respectively from the intestinal L-cells and K-cells, account for up to 70% of insulin secretory responses after nutrient ingestion [49]. In addition, GLP-1 is known to be a physiological inhibitor of glucagon secretion, while GIP can stimulate glucagon secretion [50]. Growing evidence suggests that GLP-1 promotes fatty acid oxidation, reduces lipogenesis in the liver and may increase hepatic glucose uptake [51, 52]. Furthermore, the postprandial release of GLP-1 might alter reward processes in the orbitofrontal cortex, thus exerting satiety effects [53].

##### 4.4.1. Gut microbiome

A rapidly mounting body of evidence shows that gut microbiota plays an important role in the development of IR [54]. Recent microbiota transplantation studies from insulin resistant donors to germ-free animals indicate the causal effect of microbiota [55, 56]. There is an intensive biochemical and immune "crosstalk" between gut microbiota and the host [57, 58]. On the one hand, gut microbiota may contribute to host IR in various ways, including host appetite, energy balance, fat storage, low-grade

inflammation *etc*, [59]. On the other hand, the genetics and health condition of the host can shape gut microbiota [56, 60]. Human genes, microbial genes, and diet share a complicated set of interdependencies [61, 62]. The gut microbiome may be an important target for the management of T2DM [63].

#### 4.5. Kidneys

Our understanding of T2DM has been enhanced significantly by recognition of the role of kidney glucose transporters in regulating plasma glucose levels and producing hyperglycemia. In individuals with normal glucose tolerance and a mean day long plasma glucose concentration of 100 mg/dl, all glucose is reabsorbed via sodium–glucose cotransporters SGLT1 and SGLT2 located in proximal tubule; hence no glucose is excreted in the urine [64]. While the SGLT2 is strictly localized in kidneys, the SGLT1 also is expressed in the gut, heart and lungs [64]. In healthy individuals, glucosuria may start at the plasma glucose levels of 180 mg/dl. Kidney adaptive reaction to a high level of glucose in the glomerulus is to conserve glucose by increasing glucose reabsorption through upregulation of SGLT2 expression and increased glucose transport capacity in T2DM subjects. This contributes to persistent hyperglycemia. The maximum glucose transport capacity ( $T_m$ ) of the proximal tubule on average is 375 mg/min, which roughly corresponds to 300 mg/dl plasma glucose level. In T2DM subjects, all of the filtered glucose in excess of the  $T_m$  is excreted in the urine [64-66]. Because sodium and glucose are cotransported in renal proximal tubular cells, T2DM subjects have an increase in total body sodium content and a high risk of hypertension [67]. Inhibition of SGLT-2, which is responsible for approximately 90% of renal glucose reabsorption, increases urinary glucose excretion and lowers blood glucose concentrations. SGLT-2 inhibitors improve glycemic control, reduce body weight and blood pressure, and are associated with a low risk of hypoglycemia [68]. In clinical trials, an SGLT2 inhibitor (empagliflozin) was found to have a profound effect in reducing cardiovascular and all-cause mortality in patients with T2DM and antecedents of cardiovascular disease [67]. This effect, however, was attributed mostly to a hemodynamic rather than a metabolic effect in part due to osmotic/diuretic effect of the SGLT2 and to the reduction in arterial blood pressure. Adverse events associated with SGLT-2 inhibitors include mild to moderate urinary tract and genital infections and mild dehydration, potentially leading to orthostatic hypotension [69].

#### 4.6. Brain

The brain is an insulin-sensitive organ [70]. Insulin can cross the blood-brain barrier and the insulin receptor  $\beta$  is highly expressed in neurons in different brain regions [71]. Significant changes occur in the brain signaling systems regulated by insulin, insulin-like growth factor (IGF-1), leptin, dopamine, serotonin, melanocortins and GLP-1 even at the early stages of T2DM [72]. Also, there is a growing understanding of the role that the low-density lipoprotein receptor-related protein 1 (LRP1) may play in the regulation of insulin signaling and glucose metabolism [73]. Insulin also acts on the brain, which independently suppresses lipolysis by suppression of sympathetic outflow and increases triglyceride secretion from the liver through yet unknown mechanism [37]. The brain is implicated in T2DM onset and pathology through a neuroendocrine network of appetite suppression and regulation of numerous metabolic processes [74]. The absolute majority of obese subjects either developed or have a very high risk of developing T2DM [75]. It is known that obesity results in the brain becoming resistant to a number of satiety-inducing hormones, including insulin and leptin [76-77]. Both insulin and GLP-1 decrease activity in the orbitofrontal cortex and synergistically contribute to the regulation of regional brain activity in the postprandial state [53]. Insulin regulates activity within many eating behavior-relevant regions, including areas of occipital and prefrontal cortical regions, hypothalamus, midbrain, brainstem, and regions within the striatum [76]. In addition, insulin modulates cognition, body weight, whole-body glucose, energy, and lipid metabolism [70, 78]. Metabolic abnormalities that characterize insulin-resistance syndrome may be at least partially associated with modulation of central melanocortinergic neurons that have a major impact on visceral adiposity and peripheral and hepatic insulin actions [79]. It is recognized that the functional state of the brain-signaling systems plays an important role in etiology and pathogenesis of T2DM and metabolic syndrome (MS). The pharmacological approaches controlling the brain-signaling systems regulated by insulin, IGF-1, leptin, dopamine, serotonin, melanocortins and GLP-1 can be regarded as a promising way to treat and prevent these diseases and their complications [72].

#### 4.7. Adipose tissue

It is widely recognized that adipose tissue, in addition to being a primary storage of energy, plays a very important role in body metabolism primarily through adipocyte-macrophage interaction,

releasing adiponectin, FA and the hormone leptin [80-82]. With only about 10% total systemic glucose uptake, adipose tissue may play only a minor quantitative role in postprandial glucose metabolism. On the other hand, growing evidence implicates unbalanced adipocyte metabolism and altered fat topography in the pathogenesis of glucose intolerance in T2DM [83]. Insulin suppresses adipose lipolysis hence reducing glycerol delivery to the liver and also lowering hepatic Acetyl-CoA content. Insulin also regulates basal lipoprotein lipase expression and activity of a number of other proteins [35, 37, 84]. Visceral fat deposition is the seminal factor that ultimately causes IR and the detrimental inflammatory and hormonal profile that contributes to increased risk for cardiovascular disease. Adipocyte hypertrophy and other poorly understood factors set off a pathologic adipocyte-macrophage crosstalk (Cusi 2010) resulting in adipocyte IR and the chronic release of FFA with toxic effects (lipotoxicity) in distant tissues such as muscle, liver, and pancreatic  $\beta$ -cells as well as on the heart and vascular bed [37, 85, 86]. However, 10% to 45% of the adult obese population is represented by the metabolically healthy obese individuals who possess a unique subset of characteristics that reduce metabolic and cardiovascular risk factors despite the presence of excessive fat mass [75].

#### 4.8. Endothelium: macro- and microvascular complications

In healthy individuals, the endothelium regulates a complex balance of factors that maintain vascular homeostasis and normal arterial functions, including cellular adhesion and vessel wall inflammation in addition to maintaining vasculogenesis, and angiogenesis [87]. Changes in endothelium functions are implicated in microvascular complications, such as retinopathy, neuropathy and nephropathy. A shift in the functions of the endothelium towards vasoconstriction, proinflammatory and prothrombotic states characterizes the disruption of the normal performance of endothelial cells, leading to endothelial dysfunction, which is implicated in the pathogenesis of many diseases including diabetes [88]. The last three decades of the Steno hypothesis development and recent discoveries in the field advanced deep understanding of the pathogenesis, manifestations and sequelae of global dysfunction of the vascular endothelium in diabetes mellitus [89, 90]. The hyperglycemia condition of endothelial cells, by inducing elevation of DAG,

activates PKC pathway resulting in increased oxidative stress [15, 88]. A complex array of factors is associated with the pathogenesis of endothelial dysfunction [87]. Even that causality may be not very well established; multiple pathways leading to microvasculopathy, have been characterized. They include the endothelial nitric oxide synthase (eNOS) uncoupling and NO deficiency, oxidative and nitrosative stress, lysosomal membrane permeabilization and sirtuin 1 (SIRT1) deficiency, increased production of inflammatory factors, abnormal angiogenesis, premature senescence of endothelial and endothelial progenitor cells, and disintegration of endothelial glycocalyx have been characterized [90]. There is growing interest in the modulatory role of microRNAs in diabetes-induced vascular dysfunction [87, 90]. A combination of systemic inflammation and the presence of high blood glucose concentrations is able to impair the vascular endothelium in its function, thus predisposing one to atherosclerotic disease. The enhanced oxidative stress, the increased circulating free fatty acids and the altered lipids metabolism induce heart structure damages that can also lead to diabetic cardiomyopathy [15, 91].

## 5. Contemporary treatment options for T2DM

There is an intense focus on the evidence base for optimal T2DM management with the ability to deliver effective multidisciplinary care after early diagnosis and initiate effective glucose-lowering therapies supported by structured education and self-management programs [92]. The European Association for the Study of Diabetes (Inzucchi, Bergenstal et al. 2015) and American Diabetes Association adopted a patient-centered approach that includes optimizing therapeutic options across the life span - the Chronic Care Model (CCM) for prevention and treatment of T2DM. A major barrier to optimal care is a delivery system that is often fragmented, lacks clinical information capabilities, duplicates services, and is poorly designed for the coordinated delivery of chronic care [93]. The CCM has been recognized as an effective framework for improving the quality of diabetes care, emphasizing the roles of the health care delivery team and promoting self-management on the part of the patient [93]. Lifestyle changes, which may include setting physical activity and weight loss goals, remain the initial intervention for T2DM and Medical Nutrition Therapy has become an integral component of T2DM prevention, management, and self-management education [94]. First-line therapy, involving metformin along

with lifestyle modification (diet, exercise, and weight loss), is typically low cost. However, many patients fail to meet glycemic targets on this regimen and require treatment intensification [95]. Current glycemic recommendations recognize A1C 7.0% (53 mmol/mol), preprandial capillary plasma glucose 80–130 mg/dL (4.4–7.2 mmol/L), and peak postprandial capillary plasma glucose, 180 mg/dL (10.0 mmol/L) for nonpregnant adults with diabetes.

### 5.1. Pharmacological therapy for T2DM

Although prevention of T2DM is the ideal solution and has been shown to be cost-effective in modeling studies, providing optimal cost-effective treatment to those with T2DM is an urgent medical need [95]. Given that the high costs of managing T2DM are driven in large measure by complications that are a consequence of poor glycemic control, the goal for T2DM patients is to attain and maintain glycemic control. Research shows that intensive blood glucose control can reduce the risk of T2DM complications and the cost of managing these complications over periods from 10 years to a lifetime [95]. The current approach to management of T2DM is based on the escalation of intervention based on patient response and success in glycemic control. In a recent meta-analysis, it was found that among adults with T2DM, there were no significant differences in the associations between any of nine available classes of glucose-lowering drugs (alone or in combination) and the risk of cardiovascular or all-cause mortality. Metformin was associated with lower or no significant difference in HbA1C levels compared with any other drug classes. All drugs were estimated to be effective when added to metformin [96]. Hence, metformin, if not contraindicated and if tolerated, remains the preferred initial pharmacological agent for T2DM [93, 96, 97]. However, if noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the HbA1C target over three months, dual and triple therapy may be used with combinational injectable insulin therapy considered when blood glucose is 300–350 mg/dL (16.7–19.4 mmol/L) and/or HbA1C is 10–12% (86–108 mmol/mol) [93]. The pharmacological and therapeutic implications of current drugs for T2DM were recently extensively reviewed [98, 99].

### 5.2. The need for new therapeutic agents

A recent study demonstrated that among adults with type 2 diabetes diagnosed for less than 10 years, a lifestyle intervention



compared with standard care had only limited success and resulted in a change in glycemic control that did not reach the criterion for equivalence [100]. New technologies and therapeutic options for T2DM patients are being extensively investigated [92]. Well-tolerated treatments that produce a long-lasting impact on IR are in great demand. Owing to better understanding of the pathogenesis of IR and the network of the insulin signaling pathway, as described above, several pharmacological agents have been developed to treat IR. Currently available treatments such as biguanides and thiazolidinedione are effective, but their impact may not be sustained and they have considerable adverse event profiles. Many treatments in development, which target different aspects of the insulin-signaling pathway, did not progress beyond preclinical development; others that reached clinical trials had significant adverse events and/or modest efficacy. In addition, the treatments must be specific and reversible, as many of the components of the insulin-signaling pathway are involved in other cellular functions, such as apoptosis. Despite their efficacy in treating IR, lifestyle interventions have not been embraced by patients and bariatric surgery has become quite common as a treatment option for patients with obesity [101]. There is a great need for developing a cluster of new therapeutic agents that will provide safe and sustainable improvement in IR and/or prevent comorbidities associated with T2DM. Multicomponent botanical therapeutics may play an important role in developing this type of agents.

#### **6. An approach to utilize Avicenna's heritage in the modern world.**

Avicenna remains one of the highest medical authorities for the Central Asian population. His philosophy, including a general approach to human health and healing, has a profound effect on practicing medicine by traditional healers and medical doctors alike. There are two major, sometimes interrelated, approaches for utilizing Avicenna's heritage: practicing the traditional Unani system of medicine and developing novel therapeutic agents. The Unani system of traditional medicine has been used for centuries and even though some of the practice success may be attributed to a placebo effect, it remains an important part of the health care system, particularly in rural areas of Afghanistan, Pakistan, India, Tajikistan, Mongolia, Uzbekistan, and other Central Asian countries. On the other hand, incorporating

evidence-based healing approaches into contemporary medical and pharmacological practices is a comprehensive multifaceted process [102]. This process requires an in-depth understanding of philosophy and evidence-based medicine practiced by Avicenna. Interpretation of the ancient Arabic text is a challenging problem and requires a combination of remarkable language skills, understanding of medieval medical practices and broad knowledge of modern science. One of the coauthors of a current paper (Yusuf Nuraliev) is a practicing physician and clinical pharmacologist and is also fluent in Arabic. He served as a scientific consultant for the latest translation of Avicenna's books to Russian (Dushanbe 2005 – 2015). In the course of his reading "The Canon of Medicine", he noticed that previous Russian translations of chapters devoted to diabetes recommended using "laxative remedies" that very much contradict the general understanding of disease progression and symptoms both from Avicenna's and modern points of views. Further analysis unveiled that the Arabic phrase "cleansing "wujud" (existence or inside) was interpreted as "laxative effect" or "laxative remedy." Indeed, the phrase should be interpreted as cleansing the "inside" of the organism and, most likely, could be linked to repairing the function of the endothelium [3] (Figure 1). The difficulties of translation and interpretation are particularly acute through the chapters devoted to chronic diseases and disorders including diabetes. It is not surprising that Avicenna's writing is still full of undiscovered secrets. It is necessary to combine any recent scientific research on Avicenna pharmacology, identification of medicinal plants and method of preparation. Some of the herbal preparations have been used for a long time and have good safety record. It is possible to streamline botanical therapeutics leads identification and pharmaceutical development by effective use Avicenna's heritage. In addition, complex medieval botanical preparations and individual medicinal plants can be tested against multiple new targets identified by modern science. Those botanicals can be effectively incorporated in different steps of the contemporary drug development process, including discovery and development, preclinical and clinical research, regulatory approval and post-market monitoring.

#### **7. Role of medicinal plants in diabetes treatment and prevention**

Though there are various pharmaceuticals available for prevention of metabolic syndrome and treatment of diabetes,

herbal formulations are often preferred due to low cost, fewer side effects and longer shelf life [103]. This trend is especially visible in countries with populations with a limited income and well-established practice of traditional medicine such as Tajikistan, India, Iran, Saudi Arabia, China and others [104-108]. There are attempts to validate the traditional use of medicinal plants using contemporary scientific methods [109-111]. Multiple plant species used in traditional medicine in different parts of the world have been shown to have at least some antidiabetic activity [112]. A considerable number of plants was subjected to clinical trials and found effective. Moreover, during the past few years, many bioactive phytochemicals have been isolated from hypoglycemic plants [113, 114].

Multiple mode of actions were suggested for antidiabetic medicinal plants. For example, antidiabetic actions of cocoa flavanols might contribute to prevention or delay in T2DM onset by modulating insulin secretion in pancreatic cells and targeting insulin-sensitive tissues because of their insulin-like activity or through the regulation of key proteins of the insulin-signaling pathways. Cocoa flavanols have been proved to enhance glucose uptake through the promotion of glucose transport, to repress glucose production, or to improve lipid metabolism [115]. Thirty-five plant species traditionally used by the indigenous peoples of the boreal forest in Canada for three or more symptoms of diabetes or its complications demonstrated high free-radical scavenging activity [116]. Grape polyphenols protect against metabolic syndrome by acting in the intestine to modify gut microbial community structure, resulting in lower intestinal and systemic inflammation and improved metabolic outcomes [63].

### 8. Unani system of medicine practiced by Avicenna

In the Unani system of medicine, practiced by Avicenna, a physician (healer) initially determined features of "mizaj" of a healthy person, then its changes in diseases, as well as "mizaj" of medicines, which are prescribed to correct the disease "mizaj." The mizaj was often translated as a "temperament" or sometimes as "nature" [3]. The person's mizaj consists of the balanced interaction of the four conflicting principal forces/qualities (hotness, coldness, dryness and moisture) within the elements (earth, air, water, fire) [2, 117, 118]. There are four humors (also translated as "fuel" or "juices") in the body: blood (dam); phlegm (balgham); yellow bile (safra); and black bile (sauda), each of which is associated with a pair of qualities:

hot and moist, cold and moist, hot and dry, and cold and dry, respectively. These humors form sanguineous, phlegmatic (serous), bilious (red bile), and melancholic (atrabilious) (black bile) humors (akhlat) in the body. Each individual has a dominant and subdominant temperament with all these humors existing in each individual's body.

The mizaj of a healthy person is considered as «motadil» - neutral or calm when all four properties of hotness, coldness, dryness and moisture are in harmony and proportional quantity inherent to a particular individual or organ. "Sue mizaj" or dystemperament is the deficiency and decrease in the physiologic action and reaction of the body, in a way that disturbance and dullness happen in its chemical action. Avicenna described 16 distinct types of disorders of temperament (called by names such as sue mizaj, inequable temperament, intemperament, dyscrasias), which cause sue mizaj gheiremotadil, or imbalance in the body.

Treatment is aimed directly at restoring balance or equilibrium of various elements, humors and faculties to the patient's temperament or humors. Individualized treatment relies on the psychophysiological physique of the patient. Avicenna states, "Truly, when the quality of the disease is understood, it is necessary to choose a medicine with the opposite quality, for the disease is treated with opposition" [118]. The physician's task was to restore the balance of disturbed mizaj to the level of «motadil», *i.e.* "balanced nature" by means of suitable medications. A single drug should not be used to treat one and the same disease. Indeed, Avicenna warned that when treating diabetes, one should not take the same medicine with long (and repeated courses) treatment. The treatment must include the six factors to ensure that, not only are the symptoms treated, but the causes of illnesses are also focused upon. While modern medicine often aims at controlling symptoms and managing illnesses, the Unani system of medicine aims at curing illnesses and managing health [117]. Different ideas about treatment, or ilaj, introduced in traditional medicine, are grouped as ilaj-bil-Tadbeer (regimental therapy), ilaj-bil-Ghiza (dietotherapy), ilaj-bil-Dawa (pharmacotherapy) and ilaj-bil-Yad (surgery) [117].

### 9. Methods of diabetes treatment used by Avicenna

Ethnobotanical studies in Central Asia report that the local population still broadly uses medicinal plants in treating T2DM [119]. Many modern folk healers and even physicians, involved

in the treatment of diabetes, keep secret the remedies and therapy methods used for the management of the disease. If asked what they use to treat diabetes, the healers usually do not provide direct answers or just say that they use techniques of Avicenna or other well-known ancient authorities.

For the purpose of this article, we mostly concentrated on the materials from "The Canon of Medicine" and the treatise Al-Vohiya or Faiziya (from the Arabic word "vohiya" or code and from the Tajik word "faiziya" or good) — "Code of Recipes" or "Useful Recipes." The latter work presents a kind of pharmacotherapeutic guide for the use of simple medicines, depending on the character of their therapeutic effect manifestations in the treatment of certain diseases [4, 120]. Avicenna used in "The Canon of Medicine" techniques and methods based on advances in the scientific and medical terminology of his era. He describes cleansing, cooling, decontamination therapy and treatment with the principles of "opposite with opposite" and "like with like." Several hundred substances and receipts from different sources are mentioned for treatment of different illnesses in the Canon [121]. Avicenna described the condition of plant collection and storage, which guaranteed the quality of primary materials [122].

Thus far, most medicinal substances prescribed by Avicenna remain largely unexamined. When prescribing individual herbal remedies, Avicenna often gave only the name of the medicinal herb, or the therapeutic form. In some cases, he provided a very short description, for example, prescribing the powder from the leaves or dried fruits of a particular plant, or from roots of a certain tree in a dose of 0.5 or more dirhams, so many times per day. A physician unfamiliar with the basics of ancient medical terminology does not know how many grams or milligrams correspond to 0.5 dirham (about 1.5 gram). In Avicenna's literary works, many recipes provide only the generic name of the plant, such as powder from the leaves of mint or oregano. However, each of these plants includes multiple varieties growing in various geobotanical areas on different continents. Given these obstacles, only a trained professional can accurately select the desired plant species. The medieval medico-biological terminology associated with the teaching of mizaj, mizaj-diagnostics and mizaj-therapy present additional challenges for interpreting Avicenna's approach to treating various diseases.

An in-depth analysis of Avicenna's writings reveals that he considered that, in diabetes, the character of mizaj changes to the "cold" side. In modern understanding, this may refer to a shift of

pH of the body fluids towards acidosis. Under the influence of the products with the "cold nature," according to Avicenna, there is a significant change of the mizaj of internal environment to the cold, *i.e.* acidic direction, primary in endothelium, as well as in the kidneys and liver, leading to diabetes. Avicenna often defined character mizaj of drugs by their organoleptic and physical parameters, such as taste, smell, color and consistency. In the treatment of patients, he demonstrated a very rigorous approach to determining the character of the mizaj of the human body as a whole, the character of changes of the patient's body mizaj, as well as the character of the mizaj of prescribed medicines. In accordance with the classification in the Unani system of medicine, most remedies have a simple nature: hot, cold, dry or wet. Combinations of these properties define complex mizaj.

Avicenna describes two different tactics in treating patients: "like with like" and "opposite with opposite" [118]. According to Avicenna, the therapy tactics "like with like," *i.e.* treatment of cold acidosis by means of cold acidic agents was unacceptable, as it promoted deterioration of the patient [123]. Consequently, Avicenna prohibited the prescribing of acidic foods and beverages in diabetes, realizing that these foods aggravate the shift of patient mizaj to the cold diabetogenic side [124]. The therapy tactics "opposite with opposite," *i.e.* treatment of acidosis status by using alkalizing agents, is the basis of diabetes therapy by Avicenna. In the basis of Avicenna's medicinal remedies intended for pathogenic and adjuvant (accessory) therapy of different degrees and forms of diabetes were vegetables, minerals and animal products with alkalizing properties, which fully corresponds to the therapy tactics "opposite with opposite" [125].

Avicenna emphasized that mizaj is an inherent property of the person and the knowledge of the characteristics of mizaj allows to correct its deviations occurring in various diseases and to restore health [4]. By Avicenna's definition, "health preservation is achieved by balancing (using) certain things and avoiding others. The balance of that what should be withdrawn from the body and that what should be held in it. Avoid that what generates fatal, bad nature, hot or cold, and that what is opposed to the nature (of human) by its special property" [118].

Avicenna identified diabetes in "The Canon of Medicine" as an independent disease, having a connection with diseases of the kidneys and the liver and the pollution of all liquids of the internal environment of the organism, *i.e.*, "wujud." We

believe that in modern medicine, an understanding of wujud is consistent with the endothelium, which is recognized today as the largest endocrine organ in the body [90].

### 9.1. Evaluation of the antidiabetic treatments proposed by Avicenna

In evaluating Avicenna's treatment of diabetes, researchers at the Institute of Avicenna's Medicine and Pharmacology (IAMP, Dushanbe, Tajikistan) have concentrated on two primary characteristics of medicines: the cold mizaj corresponding to the manifestation of acidity and hot mizaj corresponding to alkalinity. A comprehensive approach is used in an analysis of Avicenna's treatment and prevention of diabetes. To identify plants, minerals and animal products suggested by Avicenna for diabetes treatment and prevention multiple sources, including publications in English, Russian, Tajik and Arabic languages were cross-referenced. Every treatment, which is aimed at correcting the violated mizaj, in general can be called mizaj-therapy, *i.e.* the predecessor of the modern pathogenical therapy in pharmacology.

As described above, there are many etiological factors contributing to the origin of pre-diabetes and IR, and they often are not interrelated. Among those factors, the manifestation of acidic properties, eventually contributing to the onset of pre-diabetes and IR, could be a common trigger [120]. Avicenna considered that the sour taste inherent in plants and food products is the main indicator of the cold mizaj. He noted that the consumption of sour (acidic) foods causes a change of mizaj of the human body to the cold (sour, acidic) *i.e.* diabetogenic side.

A growing pool of evidence suggests that a diet with high acid load increases body acidity and may be an independent predictor of developing IR and T2DM [126]. Higher acidic dietary acid-base load, defined by higher the potential renal acid load and net endogenous acid production scores, may be an independent risk factor for the development of IR and related metabolic disorders [127, 128]. Mild metabolic acidosis, measured by plasma lactate, aligns with insulin resistance independent of obesity and is induced by short-term increases in energy and dietary acid load in healthy humans [129]. In large prospective cohort studies, a high dietary acid load was positively associated with T2DM risk and found to be independent of other known risk factors for diabetes [130-132]. Meta-analysis of the

three prospective cohort studies further confirmed that, after adjustment for other diabetes risk factors, a higher dietary acid load is associated with an increased risk of T2DM [133].

In our experiments, supplementation of the diet with a daily gavage of 5 ml/kg fresh lemon juice in rabbits for two weeks resulted in changes associated with diabetogenesis. Blood and urine pH was reduced 6.2% and 16.9% respectively, and the glucose level in blood increased 58.1% and HbA1c increased 72.3%. In addition to mild acidosis, physiological and biochemical changes showed the development of IR and associated modifications of liver and kidney functions [124]. We also showed that six acidic products included in the diabetogenic risk factors by Avicenna have pharmacological and biochemical effects on the organism of laboratory animals consistent with the development of diabetes [6].

Following his predecessors, Avicenna considered that thirst and polyuria are the main symptoms of diabetes, and noted, "in the urine of patients with diabetes a substance resembling honey to taste." Antidiabetic agents, which have been used during that historical period, mainly were evaluated according to the manifestation of their thirst-quenching effect [134, 135]. Pharmacological and biochemical screening conducted at IAMP showed that medicinal plants recommended by Avicenna have not only thirst-quenching action but also a hypoglycemic effect (data not shown). This relationship is also noted by modern studies [136].

In the opinion of Avicenna, all dysmetabolic processes in diabetes are the result of dysfunctions in the three main organs: the endothelium, kidneys and liver. In his doctrine, Avicenna pays special attention to developing common drug therapy tactics for diabetes, especially onllaj-bil-Ghiza (dietotherapy). Developed by Avicenna the tactic of diabetes therapy encompassed all major pathogenic disturbances observed in the kidneys, liver and endothelium in the early stages of the disease, *i.e.* it is focused entirely on the elimination of the state of pre-diabetes.

As an experienced physician practicing evidence-based medicine, Avicenna prescribed medication that can correct the disorders of water metabolism (thirst-quenching) and changes in the cardiovascular and nervous systems, as well as the internal organs [137]. Tactics of treatment of diabetes by Avicenna targeted correcting the process of diabetogenesis itself and impaired renal function and liver, which perform excretory functions, *i.e.* correction of acid-base status. Thus, these therapy

tactics restored numerous functions of the endothelium.

Simple and complex anti-diabetic herbal remedies recommended by Avicenna are of particular interest. All medicines and medicinal plants are characterized by Avicenna in the framework of the mizaj doctrine and in accordance with the requirements of the two ancient pharmacological laws—therapy tactics “opposite with opposite” and “like with like.” The fact that all recommended antidiabetic agents were of natural origin is another distinctive feature of Avicenna’s medical tactics in comparison with the modern approaches to diabetes treatment. Those agents had low toxicity and did not cause adverse effects on the liver, kidneys and other internal organs. Moreover, their curative effect was aimed at restoring normal organs functions, as well as contributing to the purification of body fluids and the endothelium.

## 9.2. Natural products used to treat diabetes

We have compiled a list of medicinal plants, minerals and animal products recommended by Avicenna for etiopathogenetic, auxiliary and symptomatic treatment of diabetes and related diseases. We identified Russian and Latin names of medicinal plants recommended by Avicenna as antidiabetic agents. We used a combination of medieval and contemporary sources to identify plants including the “Tajik Thesaurus Medical Dictionary at-Tanvir” of Kamari Bukhari (X century); “Kitab Saydana” (Pharmacognosy) of Abu Rayhan Beruni and “Hakoik-ul-adviya” (Pharmacopoeia) of Abumansur Muwafaq Ali Hiravi (X century). Latin names of 75 medicinal plants were confirmed based on the description and cross-referenced in the “International Code of Botanical Nomenclature” and multi-volume “Flora of Bulgaria and the Soviet Union [138].” We consulted web-based databases, including International Plant Names Index; U.S. Department of Agriculture, Agricultural Research Service, Beltsville Area; Biodiversity Heritage Library; Royal Botanical Gardens Kew; Royal Botanical Gardens Edinburgh; European Environment Agency; Integrated Taxonomic Information System; and Tropicos. The list of most common antidiabetic plants is presented list of plant species most commonly referred by Avicenna for diabetes treatment: *Acacia arabica* (Lam.) Willd., *Acacia nilotica* (L.) Delile, *Alhagimaurorum* Medik., *Aloe vera* L., *Alpinia officinarum* Hance, *Althaea officinalis* L., *Armeniaca vulgaris* Lam., *Artemisia* L. multiple species, *Astragalustragacantha* L., *Berberis vulgaris* L., *Boswelliacarteri* Birdw., *Cerasus vulgaris* Mill.,

*Chamomillarecutita* (L.) Rauschert, *Cinnamomum cassia* (L.) J. Presl, *Cistus ladaniferus* Curtis, *Citrus limon* (L.) Burm. Fil., *Commiphoramyrrrha* Engl., *Coriandrum sativum* L., *Crocus sativus* L., *Cucumis sativus* L., *Cucurbita maxima* Duchesne, *Cupressus sempervirens* L., *Cydonia oblonga* Mill., *Cynarascolymus* L., *Cyperus rotundus* L., *Daucus carota* L., *Ecballium elaterium* (L.) A. Rich., *Ferula foetida* Regel, *Foeniculum vulgare* Mill., *Geranium collinum* Stephan ex Willd., *Glycyrrhiza glabra* L., *Hordeum vulgare* L., *Hypericum perforatum* L., *Iris germanica* L., *Lactuca scariola* L., *Malabailapumila* Boiss., *Matricaria chamomilla* L., *Mentha arvensis* L., *Nymphaea alba* L., *Origanum dictamnus* L., *Phaseolus vulgaris* L., *Pimpinella anisum* L., *Plantago psyllium* L., *Portulaca oleracea* L., *Potentilla reptans* L., *Prunus domestica* L., *Punicagranatum* L., *Pyrus communis* L., *Rhus coriaria* L., *Rosa cinnamomea* L., *Rosa damascena* P. Mill., *Silybum marianum* (L.) Gaertn., *Syzygium aromaticum* (L.) Merr. & L. M. Perry, *Thymus glaber* Mill., *Triticum aestivum* L., *Triticum vulgare* Vill., *Viola odorata* L., *Vitis vinifera* L.,

The arsenal of medicines that Avicenna recommended for diabetes therapy included 84 agents. Plant products accounted for 75 items (89.3%), animal six (7.1%), and mineral tree, (3.6%). Depending on the natural product properties was performed either on herbal infusion (1 plant material:10 water), or freshly collected sap, or fresh juices (fruits). We measured pH and evaluated the concentration of alkaline (potassium, sodium, magnesium) and acidic ( $\text{Cl}^-$ ,  $\text{PO}_4^{3-}$ ,  $\text{SO}_4^{2-}$ ) equivalents and some organic acids. Using these results, we classified all 84 antidiabetic herbs and animal and mineral agents in two groups: acidic (cold mizaj) and alkaline (hot mizaj). The absolute majority of tested substances (92%) belonged to alkaline (hot mizaj). This includes all of the mineral and plant products with the exception of the fruit juice of two plant species, *Rosa cinnamomea* L. (cinnamon rose, pH 1.8-2.8) and *Citrus limon* (L.) Burm. Fil. (lemon, pH around 2.3-3.4).

The results of the scientific analysis of Avicenna’s doctrine, dedicated to the issues of ilaj-bil-Tadbeer, Ilaj-bil-Ghiza and Ilaj-bil-Dawa of diabetes, showed that in the first place, Avicenna recommended diet correction (Ilaj-bil-Ghiza) and then medicinal treatment. Along with simple vegetable, animal and mineral remedies (Ilaj-bil-Dawa), Avicenna used 20 complex products consisting of two or more components for the treatment of severe forms of diabetes.

### 9.3. Developing botanical therapeutics based on Avicenna's ideas

Our preliminary analysis showed that in ecologically clean mountainous regions of Tajikistan, more than 40 species of medicinal plants with active metabolism corrective properties, including antidiabetic, are growing. Many polyphenol- and flavonoid-containing plants have, along with a hypoglycemic effect, active hepatoprotective, nephroprotective, antioxidant, angioprotective, immunostimulant or adaptogenic effects. Therefore, creation of new plant polyphenols containing herbal remedies may provide fundamentally new effective antidiabetic agents with metabolism-corrective effects, improving liver, kidney, and pancreas functioning (Figure 1), as well as actively suspending the process of diabetogenesis. Widely distributed in Tajikistan, *G. collinum* is a medicinal plant mentioned by Avicenna for diabetes treatment and has been used in traditional medicine for the treatment of rheumatism, gout, dysentery, skin wounds, eczema and external and internal bleeding. The plant's total polyphenolic compounds 349.84 mg GAE/g, flavonoids 96.07 mg QE/g, antioxidant activity  $IC_{50}$  11.21  $\mu$ g/mL, antidiabetic activity (PTP-1B)  $IC_{50}$  0.10  $\mu$ g/mL and ( $\alpha$ -Glucosidase)  $IC_{50}$  0.07  $\mu$ g/mL were measured using a 50% aqueous-ethanolic extract. In addition 10 biologically active compounds were elucidated from the root of *G. collinum* by analyzing their spectral data (MS,  $^1H$  and  $^{13}C$ -NMR, including HMQC, HMBC and DEPT): 3,3',4,4'-tetra-O-methylellagic acid, 3,3'-di-O-methylellagic acid, caffeic acid, quercetin, (+)-catechin, (-)-epicatechin, (-)-epigallocatechin, gallic acid,  $\beta$ -sitosterol-3-O- $\beta$ -D-glucopyranoside and corilagin [114].

Within the framework of Avicenna's approach to diabetes management new botanical therapeutics have been developed at IAMP. For example, Novobet, a concoction of roots of *G. collinum*, *G. glabra* and fruits of *R. coriaria*, in alloxan-induced diabetic rabbits demonstrated significant activity in reducing hyperglycemia. An oral dose of 5 ml/kg Novobet infusion resulted, at seven, 15 and 30 days of treatment, in serum glucose level reductions, compared with untreated animals. In addition, serum concentration of total lipids, cholesterol, triglycerides and malondialdehyde decreased and HDL level increased [139].

### Conclusion and discussion.

Even a millennium later, we have a lot to learn from the evidence-based medical approach of Avicenna [3, 6, 117]. A conventional, comprehensive approach to the prevention and treatment of diabetes relies on a growing understanding of glucose metabolism and regulatory pathways (Figure 1). Multiple glucose-reducing medicines differ in efficacy, ease of use, negative side effects and cost. The potential of a therapy "cost" involves more than just a cost-benefit analysis. It is based on the set of attributes that takes into account the long-term safety and tolerability, risk of hypoglycemia, weight gain and suitability of using it in a presence of comorbidities. Individualized therapy should take into account the needs and preferences of patients, based on their circumstances, their understanding and their commitment. Now, as in Avicenna's times, for tolerant, adequate pharmacotherapy, an individual approach is required to assess goals of treatment and to achieve them in the safest way. Consequently, for the purposes of effective treatment of T2DM and prevention of severe complications we need to integrate Western and complementary medicines.

In both in Avicenna's and contemporary approaches, diet plays a major role in the prevention and management of diabetes. Plant-based foods such as fruits and vegetables are a key source of potassium and magnesium, major contributors to the dietary alkali load. Numerous studies have reported the putative association of the consumption of specific food products, or their constituents, with the incidence of diabetes, and mounting evidence now suggests that some dietary factors can improve glycemic regulation. Foods and dietary constituents have been shown to act through multiple pathways and may exhibit a variety of modes of action including inhibition of carbohydrate-hydrolyzing enzymes, intestinal glucose transport, hepatic glucose output, delay of gastric emptying and/or intestinal absorption of carbohydrates [140, 141]. Food products and dietary constituents may modulate the incretin effect, stimulate glucagon-like peptide-1 (GLP-1) secretion or inhibit dipeptidyl peptidase-IV (DPP-IV). Some dietary constituents mimic insulin action, affect insulin release or sensitivity, or inhibit protein tyrosine phosphatase 1B (PTP1B). They also may activate the peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ), demonstrate insulin mimetic action or stimulate insulin secretion [141].

The majority of medicinal plants have never been tested against ever-growing numbers of molecular targets (Figure 1). Medicinal plants are multifaceted, adaptive, environmentally interactive systems exhibiting synergy and nonlinear healing causality [142]. Recently, Western science and indigenous science appear as equally valid notions to guide emergent research practices [110]. Many herbal medicines are now being supported by scientific evidence and have been shown to exert significant effects in the body, relieve symptoms, treat disease and improve everyday function. Diverse natural compounds have been shown to affect cardiovascular and metabolic disorders via different mechanisms, such as anti-inflammatory activity, improvement of blood lipid profiles, improvement of insulin sensitivity, or normalization of blood glucose levels. However, only a few molecular targets or pathways are well-established to mediate the beneficial effects of natural compounds in the context of cardiovascular and metabolic disorders. Selected examples include the AMP-activated protein kinase (AMPK), cyclooxygenase (COX)-1 and -2, the dipeptidyl peptidase-4 (DPP-4), eNOS, the transcription factors NF- $\kappa$ B, nuclear factor-erythroid 2-related factor 2 (Nrf2), and PPAR, the PTP1B, and 5-lipoxygenase (5-LO) [143, 144]. For a variety of medicinal plants used in many traditional medicines, the mechanisms of action have not yet been elucidated. Scientists routinely accumulate large sets of data produced by advanced technologies. Hence, computational approaches and advanced synthetic techniques may be effectively utilized in developing botanical therapeutics [111].

A recent review summarized that medicinal plants used in Persian medicine, including many used by Avicenna for prevention and treatment of diabetes performed their therapeutic effects via various well-established pharmacological mechanisms of actions. Established modes of actions encompass multiple cellular mechanisms, including regeneration of pancreatic  $\beta$ -cell, limitation of glycogen degradation and gluconeogenesis and anti-inflammatory, immunoregulatory, antiapoptosis, antioxidative stress, as well as modulation of intracellular signaling transduction pathways [145]. In the current paper, we also demonstrated how an in-depth analysis and new interpretations of the 1,000-year-old text may lead to new approaches to the search for diabetes prevention and treatment. Naturally, the efficacy of medicinal herbs needs to be established, and toxicity, contraindications and side effects also

need to be investigated. This is best done with clinical research and trials that are being conducted almost exclusively on efficacy and are limited in number, probably because of a lack of funding. Very little to no attention is being given to more traditional fresh herbal extracts [146].

It is essential to monitor the quality of botanical therapeutics and adapt the use of medicinal plants to modern conditions. The quality of the botanicals can be significantly improved by implementing good agricultural practices at the point of cultivation of medicinal plants and good practices during the manufacturing and packaging of finished herbal products, as well as post-marketing quality-assurance surveillance [147]. Clinical evaluation of botanical therapeutics remains an important issue. Collaborative partnerships offer the context and process by which many of the ethical challenges in international herbal medicine research can be resolved [148]. The Fogarty International Center of the National Institutes of Health plays an important role in cross-training investigators and investing in safety-monitoring infrastructure, which helps promote ethical international herbal medicine research. Comprehensive analysis of Avicenna's approach to the treatment of prediabetes and diabetes provides valuable directions in the search for plant-based treatments. Botanical therapeutics may provide relatively inexpensive, safe methods for diabetes treatment. This is even more important for developing countries with limited resources.

## References

1. Tulgaa Kh. Emerging challenges in healthcare in Central Asia. *Cent Asian J Med Sci* 2015; 1: 1-4.
2. Abu-Asab M, Amri H, Micozzi M. *Avicenna's medicine: a new translation of the 11th-century canon with practical applications for integrative health care*. Rochester, Vermont: Healing Art Press; 2013. p 1-462.
3. Aisa H, Nuraliev Y, Maidina H, Sharofova M, Bahromova Z. Contribution of Ibn Sina (Avicenna) to the therapy of vitiligo. Dushanbe, Tajikistan: Urumqi; 2015. p 1-342.
4. Nuraliev Y. *Medical system of Avicenna*. Dushanbe, Tajikistan: Donish; 2005. p 1-300 (In Russian).
5. Nasser M, Tibi A, Savage-Smith E. Ibn Sina's Canon of Medicine: 11th century rules for assessing the effects of drugs. *J R Soc Med* 2009; 102: 78-80.
6. Nuraliev Y, Sharofova M, Ganiev K. Diabetogenic risk

- factors by Avicenna. Dushanbe, Tajikistan: Contrast; 2013. p 1-184 (In Russian).
7. World Health Organization. Global report on diabetes. Geneva, Switzerland: WHO Press; 2016. p 1-88.
  8. Centers for Disease Control and Prevention. National diabetes statistics report: estimates of diabetes and its burden in the United States, 2017. [accessed on 21 July 2017]. Available at: [www.cdc.gov](http://www.cdc.gov).
  9. Bragg F, Holmes M, Iona A, Guo Y, Du H, Chen Y, et al. Association between diabetes and cause-specific mortality in rural and urban areas of China. *JAMA* 2017; 317: 280-9.
  10. Tumenbayar B. Diabetes control in Mongolia: facts and needs. *Cent Asian J Med Sci* 2016; 2: 109-10.
  11. IDF. IDF diabetes atlas [accessed on 21 July 2017]. Available at: [www.diabetesatlas.org](http://www.diabetesatlas.org).
  12. Ebers Papyrus. Das hermetische Buch über die Arzneimittel der alten Aegypter von Georg Ebers. Leipzig, Deutschland: Engelmann; 1875.
  13. Trevisanato S. The dawn of clinical medicine: Bronze age medical practice in Egypt. *Int J Hist & Phil Med* 2012; 1-9.
  14. Karamanou M, Protogerou A, Tsoucalas G, Androutsos G, Poulakou-Rebelakou E. Milestones in the history of diabetes mellitus: The main contributors. *World J Diabetes* 2016; 7: 1-7.
  15. Panigrahy S, Bhatt R, Kumar A. Reactive oxygen species: sources, consequences and targeted therapy in type 2 diabetes. *J Drug Target* 2017; 25: 93-101.
  16. Abdul-Ghani M. Type 2 diabetes and the evolving paradigm in glucose regulation. *Am J Manag Care* 2013; 19: S43-50.
  17. Zaccardi F, Webb D, Yates T, Davies M. Pathophysiology of type 1 and type 2 diabetes mellitus: a 90-year perspective. *Postgrad Med J* 2015: 1-7.
  18. Erickson S, Le L, Zakharyan A, Stockl K, Harada A, Borson S, et al. New-Onset Treatment-Dependent Diabetes Mellitus and Hyperlipidemia Associated with Atypical Antipsychotic Use in Older Adults without Schizophrenia or Bipolar Disorder. *J Am Geriatr Soc* 2012; 60: 474-9.
  19. Chen X, Yang W. Branched-chain amino acids and the association with type 2 diabetes. *J Diabetes Investig* 2015; 6: 369-70.
  20. Guay C, Regazzi R. Circulating microRNAs as novel biomarkers for diabetes mellitus. *Nat Rev Endocrinol* 2013; 9: 513-21.
  21. Saini V. Molecular mechanisms of insulin resistance in type 2 diabetes mellitus. *World J Diabetes* 2010; 1: 68.
  22. Samuel V, Shulman G. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. *J Clin Invest* 2016; 126: 12-22.
  23. Gilbert M, Lkhagvasuren E, Boldbaatar D, Magnan C. The regulation of energy metabolism: an Important facet of P53 function. *Cent Asian J Med Sci* 2017; 3: 106-15.
  24. Yang Q, Graham TE, Mody N, Preitner F, Peroni O, Zabolotny J, et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature* 2005; 436: 356-62.
  25. Park S, Park CY, Sweeney G. Biomarkers of insulin sensitivity and insulin resistance: Past, present and future. *Crit Rev Clin Lab Sci* 2015; 52: 180-90.
  26. Barazzoni R, Zanetti M, Ferreira C, Vinci P, Pirulli A, Mucci M, et al. Relationships between desacylated and acylated ghrelin and insulin sensitivity in the metabolic syndrome. *J Clin Endocrinol Metab* 2007; 92: 3935-40.
  27. Kanbay M, Jensen T, Solak Y, Le M, Roncal-Jimenez C, Rivard C, et al. Uric acid in metabolic syndrome: From an innocent bystander to a central player. *Eur J Intern Med* 2016; 29: 3-8.
  28. Lotta L, Sharp S, Burgess S, Perry J, Stewart I, Willems S, et al. Association Between Low-Density Lipoprotein Cholesterol-Lowering Genetic Variants and Risk of Type 2 Diabetes: A Meta-analysis. *JAMA* 2016; 316: 1383-91.
  29. Chuluun-Erdene A, Dagdan B, Sengeragcha O, Sanjmyatav P, Janlav M. Association of apolipoprotein A-V gene polymorphisms and lipid metabolism in Mongolian patients with metabolic syndrome. *Cent Asian J Med Sci* 2017; 3: 140-7.
  30. Cantley LC. The phosphoinositide 3-kinase pathway. *Science* 2002; 296: 1655-7.
  31. Affourtit C. Mitochondrial involvement in skeletal muscle insulin resistance: A case of imbalanced bioenergetics. *BBA-Bioenergetics* 2016; 1857: 1678-93.
  32. Jeon SM. Regulation and function of AMPK in physiology and diseases. *Exp Mol Med*, 2016. doi: 10.1038/emm.2016.81.
  33. Szendroedi J, Yoshimura T, Phielix E, Koliaki C, Marcucci M, Zhang D, et al. Role of diacylglycerol activation of PKCO



- in lipid-induced muscle insulin resistance in humans. *Proc Natl Acad Sci USA* 2014; 111: 9597-602.
34. Ritter O, Jelenik T, Roden M. Lipid-mediated muscle insulin resistance: different fat, different pathways? *J Mol Med* 2015; 93: 831-43.
  35. Perry RJ, Camporez JPG, Kursawe R, Titchenell PM, Zhang D, Perry CJ, et al. Hepatic acetyl CoA links adipose tissue inflammation to hepatic insulin resistance and type 2 diabetes. *Cell* 2015; 160: 745-58.
  36. Magkos F, Su X, Bradley D, Fabbrini E, Conte C, Eagon JC, et al. Intrahepatic diacylglycerol content is associated with hepatic insulin resistance in obese subjects. *Gastroenterology* 2012; 142: 1444-6.
  37. Ferris HA, Kahn CR. Unraveling the Paradox of Selective Insulin Resistance in the Liver: the Brain–Liver Connection. *Diabetes* 2016; 65: 1481-3.
  38. Marchetti P, Bugliani M, Boggi U, Masini M, Marselli L. The pancreatic  $\beta$  cells in human type 2 diabetes. in *Diabetes*. New York, USA: Springer; 2013. p 288-309.
  39. Meier J, Bonadonna R. Role of reduced  $\beta$ -cell mass versus impaired  $\beta$ -cell function in the pathogenesis of type 2 diabetes. *Diabetes care* 2013; 36: S113-9.
  40. Saisho Y.  $\beta$ -cell dysfunction: Its critical role in prevention and management of type 2 diabetes. *World J Diabetes* 2015; 6: 109-24.
  41. DeFronzo R. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 2009; 58: 773-95.
  42. Lee Y, Wang MY, Yu XX, Unger R. Glucagon is the key factor in the development of diabetes. *Diabetologia* 2016; 59: 1372-5.
  43. Lund A, Bagger J, Christensen M, Knop F, Vilsbøll T. Glucagon and type 2 diabetes: the return of the alpha cell. *Curr Diab Rep* 2014; 14: 1-7.
  44. Longuet C, Sinclair E, Maida A, Baggio L, Maziarz M, Charron M, et al. The glucagon receptor is required for the adaptive metabolic response to fasting. *Cell metab* 2008; 8: 359-71.
  45. Dunning B, Foley J, Ahrén B. Alpha cell function in health and disease: influence of glucagon-like peptide-1. *Diabetologia* 2005; 48: 1700-13.
  46. Sandoval D, D'Alessio D. Physiology of proglucagon peptides: role of glucagon and GLP-1 in health and disease. *Physiol Rev* 2015; 95: 513-48.
  47. Davidson J, Holland W, Roth M, Wang My, Lee Y, Yu X, et al. Glucagon therapeutics, dawn of a new era for diabetes care. *Diabetes Metab Res Rev* 2016; 32: 660-5.
  48. Drucker D, Nauck M. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *The Lancet* 2006; 368: 1696-705.
  49. Holst J, Vilsbøll T, Deacon C. The incretin system and its role in type 2 diabetes mellitus. *Mol Cell Endocrinol* 2009; 297: 127-36.
  50. Nauck M. Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Diabetes Obes Metab* 2016: 203-16.
  51. Svegliati-Baroni G, Saccomanno S, Rychlicki C, Agostinelli L, De Minicis S, Candelaresi C, et al. Glucagon-like peptide-1 receptor activation stimulates hepatic lipid oxidation and restores hepatic signalling alteration induced by a high-fat diet in nonalcoholic steatohepatitis. *Liver Int* 2011; 31: 1285-97.
  52. Watanabe T, Tamura Y, Kakehi S, Funayama T, Gastaldelli A, Takeno K, et al. Effects of sitagliptin on ectopic fat contents and glucose metabolism in type 2 diabetic patients with fatty liver: A pilot study. *J Diabetes Investig* 2015; 6: 164-72.
  53. Heni M, Kullmann S, Gallwitz B, Häring HU, Preissl H, Fritsche A. Dissociation of GLP-1 and insulin association with food processing in the brain: GLP-1 sensitivity despite insulin resistance in obese humans. *Mol Metab* 2015; 4: 971-6.
  54. Vijay-Kumar M, Aitken J, Carvalho F, Cullender T, Mwangi S, Srinivasan S, et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science* 2010; 328: 228-31.
  55. Zhang L, Bahl M, Roager H, Fonvig C, Hellgren L, Frandsen H, et al. Environmental spread of microbes impacts the development of metabolic phenotypes in mice transplanted with microbial communities from humans. *ISME J* 2017; 11: 676-90.
  56. Goodrich J, Waters J, Poole A, Sutter J, Koren O, Blekhman R, et al. Human genetics shape the gut microbiome. *Cell* 2014; 159: 789-99.

57. Bordenstein S, Theis K. Host biology in light of the microbiome: ten principles of holobionts and hologenomes. *PLoS Biol*, 2015. 10.1371/journal.pbio.1002226.
58. Wahlström A, Sayin SI, Marschall HU, Bäckhed F. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. *Cell Metab* 2016; 24: 41-50.
59. Woting A, Blaut M. The Intestinal Microbiota in Metabolic Disease. *Nutrients*, 2016. 10.3390/nu8040202.
60. Ussar S, Fujisaka S, Kahn C. Interactions between host genetics and gut microbiome in diabetes and metabolic syndrome. *Mol Metab* 2016; 5: 795-803.
61. Komaroff A. The Microbiome and Risk for Obesity and Diabetes. *JAMA* 2017; 317: 355-6.
62. Evans D, Hirsch J, Dushenkov S. Phenolics, inflammation, and nutrigenomics. *J Sci Food Agric* 2006; 86: 2503-9.
63. Roopchand D, Carmody R, Kuhn P, Moskal K, Rojas-Silva P, Turnbaugh P, et al. Dietary Polyphenols Promote Growth of the Gut Bacterium *Akkermansia muciniphila* and Attenuate High-Fat Diet-Induced Metabolic Syndrome. *Diabetes* 2015; 64: 2847-58.
64. Wright E, Loo D, Hirayama B. Biology of human sodium glucose transporters. *Physiol rev* 2011; 91: 733-94.
65. Kamran M, Peterson R, Dominguez J. Overexpression of GLUT2 gene in renal proximal tubules of diabetic Zucker rats. *J Am Soc Nephrol* 1997; 8: 943-8.
66. Farber S, Berger E, Earle D. Effect of diabetes and insulin on the maximum capacity of the renal tubules to reabsorb glucose. *J Clin Invest* 1951; 30: 125-9.
67. Scheen A. Effects of reducing blood pressure on cardiovascular outcomes and mortality in patients with type 2 diabetes: Focus on SGLT2 inhibitors and EMPA-REG OUTCOME. *Diabetes Res Clin Pract* 2016; 121: 204-14.
68. Kimura G. Importance of inhibiting sodium-glucose cotransporter and its compelling indication in type 2 diabetes: pathophysiological hypothesis. *J Am Soc Hypertens* 2016; 10: 271-8.
69. Schwartz S, Ahmed I. Sodium-Glucose Cotransporter-2 Inhibitors: An Evidence-Based Practice Approach to Their Use in the Natural History of Type 2 Diabetes. *Curr Med Res Opin* 2016; 32: 907-19.
70. Heni M, Kullmann S, Preissl H, Fritsche A, Häring HU. Impaired insulin action in the human brain: causes and metabolic consequences. *Nat Rev Endocrinol* 2015; 11: 701-11.
71. Kleinridders A, Ferris H, Cai W, Kahn CR. Insulin action in brain regulates systemic metabolism and brain function. *Diabetes* 2014; 63: 2232-43.
72. Shpakov A, Derkach K, Berstein L. Brain signaling systems in the Type 2 diabetes and metabolic syndrome: promising target to treat and prevent these diseases. *Future Sci OA*, 2015. 10.4155/fso.15.23.
73. Liu CC, Hu J, Tsai CW, Yue M, Melrose H, Kanekiyo T, et al. Neuronal LRP1 regulates glucose metabolism and insulin signaling in the brain. *J Neurosci* 2015; 35: 5851-9.
74. Myers MG, Olson DP, Low MJ, Elias CF. Brain Regulation of Feeding and Energy Homeostasis. in *Metabolic Syndrome: A Comprehensive Textbook*. New York, New York: Springer; 2016. p 347-68.
75. Gonçalves C, Glade M, Meguid M. Metabolically healthy obese individuals: Key protective factors. *Nutrition* 2016; 32: 14-20.
76. Kullmann S, Heni M, Fritsche A, Preissl H. Insulin action in the human brain: evidence from neuroimaging studies. *Journal neuroendocrinol* 2015; 27: 419-23.
77. Polyzos S, Mantzoros C. Leptin in health and disease: facts and expectations at its twentieth anniversary. *Metabolism* 2015; 64: 5-12.
78. Biessels GJ, Reagan LP. Hippocampal insulin resistance and cognitive dysfunction. *Nat Rev Neurosci* 2015; 16: 660-71.
79. Obici S, Feng Z, Tan J, Liu L, Karkaniyas G, Rossetti L. Central melanocortin receptors regulate insulin action. *J Clin Invest* 2001; 108: 1079-85.
80. DeClercq V, d'Eon B, McLeod R. Fatty acids increase adiponectin secretion through both classical and exosome pathways. *Biochim Biophys Acta*. 2015; 1851: 1123-33.
81. Park HK, Ahima R. Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. *Metabolism* 2015; 64: 24-34.
82. Dagdan B, Chuluun-Erdene A, Sengeragchaa O, Sanjmyatav P, Janlav M. Higher leptin level among Mongolians with metabolic syndrome as a predictor of cardiovascular risk. *Cent Asian J Med Sci* 2017; 3: 41-6.
83. Ng J, Azuma K, Kelley C, Pencek R, Radikova Z, Laymon C, et al. PET imaging reveals distinctive roles for different regional adipose tissue depots in systemic glucose

- metabolism in nonobese humans. *Am J Physiol Endocrinol Metab* 2012; 303: E1134-41.
84. Hegele R. Multidimensional regulation of lipoprotein lipase: impact on biochemical and cardiovascular phenotypes. *J Lipid Res* 2016; 57: 1601-7.
  85. Kolka C, Richey J, Castro A, Broussard J, Ionut V, Bergman R. Lipid-induced insulin resistance does not impair insulin access to skeletal muscle. *Am J Physiol Endocrinol Metab* 2015; 308: E1001-9.
  86. DeFronzo R. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. *Diabetologia* 2010; 53: 1270-87.
  87. Roberts A, Porter K. Cellular and molecular mechanisms of endothelial dysfunction in diabetes. *Diab Vasc Dis Res* 2013; 10: 472-82.
  88. Tabit C, Chung W, Hamburg N, Vita J. Endothelial dysfunction in diabetes mellitus: molecular mechanisms and clinical implications. *Rev Endocr Metab Disord* 2010; 11: 61-74.
  89. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. *Diabetologia* 1989; 32: 219-26.
  90. Shi Y, Vanhoutte P. Macro-and Microvascular Endothelial Dysfunction in Diabetes. *J Diabetes* 2017; 9: 434-49.
  91. Ciccone M, Scicchitano P, Cameli M, Cecere A, Cortese F, Dentamaro I, et al. Endothelial function in pre-diabetes, diabetes and diabetic cardiomyopathy: a review. *J Diabetes Metab*, 2014. doi: 10.4172/2155-6156.1000364.
  92. Chatterjee S, Khunti K, Davies M. Type 2 diabetes. *The Lancet* 2017: 2239–51.
  93. ADA. Standards of medical care in diabetes - 2016. *Diabetes Care* 2016; 39: S1-S112.
  94. Fan R, Xu M, Wang J, Zhang Z, Chen Q, Li Y, et al. Sustaining Effect of Intensive Nutritional Intervention Combined with Health Education on Dietary Behavior and Plasma Glucose in Type 2 Diabetes Mellitus Patients. *Nutrients*, 2016. doi: 10.3390/nu8090560.
  95. Liebl A, Khunti K, Orozco-Beltran D, Yale J-F. Health Economic Evaluation of Type 2 Diabetes Mellitus: A Clinical Practice Focused Review. *Clin Med Insights Endocrinol Diabetes* 2015; 8: 13-9.
  96. Palmer S, Mavridis D, Nicolucci A, Johnson D, Tonelli M, Craig J, et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes: A Meta-analysis. *JAMA* 2016; 316: 313-24.
  97. Garber A, Abrahamson M, Barzilay J, Blonde L, Bloomgarden Z, Bush M, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2017 executive summary. *Endocr Pract* 2017; 23: 207-38.
  98. Tahrani A, Barnett A, Bailey C. Pharmacology and therapeutic implications of current drugs for type 2 diabetes mellitus. *Nat Rev Endocrinol* 2016; 12: 566-92.
  99. Gaitonde P, Garhyan P, Link C, Chien J, Trame M, et al. A Comprehensive Review of Novel Drug–Disease Models in Diabetes Drug Development. *Clin Pharmacokinet* 2016; 55: 769-88.
  100. Johansen MY, MacDonald CS, Hansen KB, Karstoft K, Christensen R, Pedersen M, et al. Effect of an Intensive Lifestyle Intervention on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Trial. *Jama* 2017; 318: 637-46.
  101. Altaf QA, Barnett A, Tahrani A. Novel therapeutics for type 2 diabetes: insulin resistance. *Diabetes Obes Metab* 2015; 17: 319-34.
  102. Neumann N, Warburton D. A Review of the modern Mongolian healthcare system. *Cent Asian J Med Sci* 2015; 1: 16-21.
  103. Popović Z, Matić R, Bojović S, Stefanović M, Vidaković V. Ethnobotany and herbal medicine in modern complementary and alternative medicine: An overview of publications in the field of I&C medicine 2001–2013. *J Ethnopharmacol* 2016; 181: 182-92.
  104. Pal RS, Wal P, Pal Y, Sachan S, Kumar D, Tiwari S. A review article on: The usage of herbal medicines in the treatment of diabetes. *EJPMR* 2016; 3: 201-4.
  105. Moradi M, Asadi-Samani M, Bahmani M. Hypotensive medicinal plants according to Ethnobotanical evidence of Iran: A Systematic Review. *Int J PharmTech Res* 2016; 9: 416-26.
  106. Amiri M, Joharchi M. Ethnobotanical investigation of traditional medicinal plants commercialized in the markets of Mashhad, Iran. *Avicenna J Phytomed* 2013; 3: 254-71.
  107. Al-Ghamdi E, Qureshi N, Krekman L, Al-Ghamdi A, Al-

- Bedah A. Traditional medicine and modern medicine: Knowledge, attitude and practice of medical students and their mothers in Tabuk City, Saudi Arabia. *Br J Med Med Res* 2016; 16: 1-12.
108. Li F, Zhuo J, Liu B, Jarvis D, Long C. Ethnobotanical study on wild plants used by Lhoba people in Milin County, Tibet. *J Ethnobiol Ethnomed*, 2015. 10.1186/s13002-015-0009-3.
109. Dushenkov V, Grag B, Lila MA. Botanical therapeutics in the modern world. in *Biological characteristics of medicinal and aromatic plants and role of these plants in medicine*, Sidelnikov, NI, Editor. Moscow, Russia: FGBNU, VILAR; 2016. p 50-54.
110. Massey A, Kirk R. Bridging indigenous and western sciences. *SAGE Open*, 2015. 2158244015597726.
111. Prachayasittikul V, Worachartcheewan A, Shoombuatong W, Songtawe N, Simeon S, Prachayasittikul V, et al. Computer-aided drug design of bioactive natural products. *Curr Top Med Chem* 2015; 15: 1780-1800.
112. Giovannini P, Howes MJ, Edwards S. Medicinal plants used in the traditional management of diabetes and its sequelae in Central America: A review. *J Ethnopharmacol* 2016; 184: 58-71.
113. Jarald E, Joshi SB, Jain DC. Diabetes and herbal medicines. *Iran J Pharmacol Therap* 2008; 7: 97-106.
114. Numonov S, Edirs S, Bobakulov K, Qureshi M, Bozorov K, Sharopov F, et al. Evaluation of the Antidiabetic Activity and Chemical Composition of *Geranium collinum* Root Extracts—Computational and Experimental Investigations. *Molecules*, 2017. 10.3390/molecules22060983.
115. Martín MÁ, Goya L, Ramos S. Antidiabetic actions of cocoa flavanols. *Mol Nutr Food Res* 2016; 60: 1756-69.
116. McCune L, Johns T. Antioxidant activity in medicinal plants associated with the symptoms of diabetes mellitus used by the indigenous peoples of the North American boreal forest. *J Ethnopharmacol* 2002; 82: 197-205.
117. Miraj S, Alesaeidi S, Kiani S. A systematic review of the relationship between dystemperament (sue Mizaj) and treatments and management of diseases (Ilaj and Eslah-e-Mizaj). *Electronic Physician* 2016; 8: 3378-84.
118. Ibn Sina (Avicenna) AA. *The Canon of Medicine*. Dushanbe, Tajikistan: Donish; 2010. p 1-735 (In Russian).
119. Rezaei A, Farzadfard A, Amirahmadi A, Alemi M, Khademi M. Diabetes mellitus and its management with medicinal plants: A perspective based on Iranian research. *J ethnopharmacol* 2015; 175: 567-616.
120. Nuraliev Y, Sharofova M. *Minicannon of prediabetes*. Dushanbe, Tajikistan: Contrast; 2011. p 1-116 (In Russian).
121. Aliasl J, Khoshzaban F. Traditional herbal remedies for burn wound healing in canon of Avicenna. *Jundishapur J Nat Pharm Prod* 2013; 8: 192-6.
122. Faridi P, Zarshenas MM, Abolhassanzadeh Z, Mohagheghzadeh A. Collection and storage of medicinal plants in The Canon of Medicine. *Pharmacog J* 2010; 2: 216-8.
123. Nuraliev Y, Sharofova M, Sagdieva S. The essence of the tactics of the therapy of diabetes mellitus according to the “similar to similar” and its consequences. *Avicenna bulletin (Paemi Sino)* 2015; 3: 151-6 (In Russian).
124. Sharofova M, Nuraliev Y, Ganiev K, Suhrobov P, Zubaydova T, Samandarov N, et al. Acid dietary as diabetogenic risk factors. *Int Ed Sci Res J* 2016; 2: 51-6.
125. Sharofova M, Nuraliev Y, Sagdieva S. Tactics of diabetes treatment according to the principle “opposite with opposite” in the Avicenna’s “Canon of Medicine” and its relevance to modern medicine. *Rev Clini Pharm Drug Ther* 2015; 13: 63-8 (In Russian).
126. Della Guardia L, Roggi C, Cena H. Diet-induced acidosis and alkali supplementation. *Int J Food Sci Nutr* 2016; 67: 754-61.
127. Moghadam S, Bahadoran Z, Mirmiran P, Tohidi M, Azizi F. Association between Dietary Acid Load and Insulin Resistance: Tehran Lipid and Glucose Study. *Prev Nutr Food Sci* 2016; 21: 104-9.
128. Caruba R, Baptistella A, Paschoal V, Hübscher G. Diet-Induced Low-Grade Metabolic Acidosis and Clinical Outcomes: A Review. *Nutrients*, 2017. 10.3390/nu9060538.
129. Williams R, Heilbronn L, Chen D, Coster A, Greenfield J, Samocha-Bonet D. Dietary acid load, metabolic acidosis and insulin resistance—Lessons from cross-sectional and overfeeding studies in humans. *Clin Nutr* 2016; 35: 1084-90.
130. Williams R, Kozan P, Samocha-Bonet D. The role of dietary acid load and mild metabolic acidosis in insulin resistance in humans. *Biochimie* 2016; 124: 171-7.

131. Akter S, Kurotani K, Kashino I, Goto A, Mizoue T, Noda M, et al. High dietary acid load score is associated with increased risk of type 2 diabetes in Japanese men: The Japan Public Health Center-based prospective study. *The Journal of nutrition* 2016; 146: 1076-83.
132. Fagherazzi G, Vilier A, Bonnet F, Lajous M, Balkau B, Boutron-Ruault MC, et al. Dietary acid load and risk of type 2 diabetes: the E3N-EPIC cohort study. *Diabetologia* 2014; 57: 313-20.
133. Kieft-de Jong J, Li Y, Chen M, Curhan G, Mattei J, Malik V, et al. Diet-dependent acid load and type 2 diabetes: pooled results from three prospective cohort studies. *Diabetologia* 2017; 60: 270-9.
134. Ibn Sina (Avicenna) AA. *The Canon of Medicine*. Dushanbe, Tajikistan: Donish; 2015. p 1-1000 (In Russian).
135. Ibn Sina (Avicenna) AA. *The Canon of Medicine*. Tashkent, Uzbekistan: Fan; 1980. p 1-358 (In Russian).
136. Korsun V, Korsun E, Trumpet T, Ershov N, Ogrenich N. *Phytotherapy against diabetes. Herbs of life*. Moscow, Russia: Litres; 2016. p 1-442 (In Russian).
137. Ibn Sina (Avicenna) AA. *The Canon of Medicine*. Dushanbe, Tajikistan: Donish; 2014. p 1-1000 (In Russian).
138. McNeill J, Barrie FR, Burdet HM, Demoulin V, Hawksworth DJ, Marhold K, et al. *International Code of Botanical Nomenclature (Vienna Code) adopted by the Seventh International Botanical Congress Vienna, Austria, July 2005*. Liechtenstein A.R.G. Gantner Verlag, Ruggell; 2006. p 568.
139. Sharofova M. Effect of collection "Novobet" on metabolic processes at experimental diabetes. *Rev Clini Pharm Drug Ther* 2012; 10: 58-62 (In Russian).
140. Visavadiya N. Diabetes: updates on abnormal metabolic signaling pathways and possible medicinal plant-based targets. *Ann Food Sci Nutraceuticals* 2016; 1: 9-20.
141. Lacroix I, Li-Chan E. Overview of food products and dietary constituents with antidiabetic properties and their putative mechanisms of action: a natural approach to complement pharmacotherapy in the management of diabetes. *Mol Nutr Food Res* 2014; 58: 61-78.
142. Niemeyer K, Bell I, Koithan M. Traditional knowledge of Western herbal medicine and complex systems science. *J Herb Med* 2013; 3: 112-9.
143. Waltenberger B, Mocan A, Šmejkal K, Heiss E, Atanasov A. Natural products to counteract the epidemic of cardiovascular and metabolic disorders. *Molecules*, 2016. doi: 10.3390/molecules21060807.
144. Razavi B, Hosseinzadeh H. Saffron: a promising natural medicine in the treatment of metabolic syndrome. *J Sci Food Agric* 2016; 97: 1679-85.
145. Farzaei F, Morovati M, Farjadmand F, Farzaei M. A mechanistic review on medicinal plants used for diabetes mellitus in traditional persian medicine. *J Evid Based Complement Altern Med*, 2017. 2156587216686461.
146. Akhondzadeh S. Avicenna and evidence based medicine. *Avicenna J Med Biotechnol* 2014; 6: 1-2.
147. Chikezie P, Ojiako O. Herbal medicine: yesterday, today and tomorrow. *Altern Integr Med*, 2015. dx.doi.org/10.4172/2327-5162.1000195.
148. Tilburt J, Kaptchuk T. Herbal medicine research and global health: an ethical analysis. *Bull World Health Organ* 2008; 86: 594-9.