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Management of Type 2 Diabetes: Current Strategies, Unfocussed Aspects, Challenges, and Alternatives

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Highlights

- Type 2 diabetes is a multifactorial disorder that leads to a disturbed glucose homeostasis.
- Lifestyle management along with pharmacological approaches is crucial to achieve a successful management of diabetes.
- Complex interplays between genetics and environmental factors play important roles in the development of diabetes.
- Combinational therapies employed after failure of monotherapy result in comorbidities.
- Phytoconstituents are better alternatives owing to their multitargeting capability.

Keywords
Diabetes · Type-2 diabetes mellitus · Insulin resistance · β-cells · Genetics · Lifestyle modifications · Phytoconstituents

Abstract
Type 2 diabetes mellitus (T2DM) accounts for >90% of the cases of diabetes in adults. Resistance to insulin action is the major cause that leads to chronic hyperglycemia in diabetic patients. T2DM is the consequence of activation of multiple pathways and factors involved in insulin resistance and β-cell dysfunction. Also, the etiology of T2DM involves the complex interplay between genetics and environmental factors. This interplay can be governed efficiently by lifestyle modifications to achieve better management of diabetes. The present review aims at discussing the major factors involved in the development of T2DM that remain unfocussed during the anti-diabetic therapy. The review also focuses on lifestyle modifications that are warranted for the successful management of T2DM. In addition, it attempts to explain flaws in current strategies to combat diabetes. The employability of phytoconstituents as multitargeting molecules and their potential use as effective therapeutic adjuvants to first line hypoglycemic agents to prevent side effects caused by the synthetic drugs are also discussed.

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Introduction

Insulin resistance and β-cell dysfunction are the 2 major hallmarks of type 2 diabetes mellitus (T2DM) that appear as the result of disturbed homeostasis [1]. Failure of β-cells (~80% of their β-cell function) and insulin resistance in muscles and the liver is a vicious triumvirate responsible for the core physiological defects. However, T2DM is classically viewed as a disorder of insulin deficiency and resistance, and further insights into the pathophysiology of T2DM suggest the role of other key players in insulin deficiency and its functional inability. Pancreatic islets are composed of insulin-releasing β-cells (48–59%), glucagon-releasing α-cells (33–46%), somatostatin (SsT)-releasing δ-cells, and F cells that release polypeptides (PPs) in similar proportion [2]. Moreover, paracrine interactions occur in the sequence from β-cell to α-cells followed by δ-cells and PP-cells/F-cells [3]. While the β-cell interactions are emphasized at present, the interaction of other cells in pancreas is of crucial importance that needs to be explored further to understand their roles in glucose homeostasis [2]. Also, the development of glucose resistance in T2DM is largely influenced by fat cells (accelerated lipolysis), gastrointestinal tract (incretin deficiency/resistance), α-cells (hyperglucagonemia), kidneys (increased glucose reabsorption) and brain (insulin resistance), and complex interactions that occur between these factors and T2DM associated genes [4]. Changes in the lifestyle of T2DM patients are crucial along with pharmacological interventions to improve the overall health status of the patient. The present review discusses our current understanding of the pathogenesis of T2DM and attempts to emphasize on generally unfocused aspects of T2DM pathogenesis and treatment that may contribute significantly to treatment approaches and patient-related outcomes.

Understanding the Diabetes Machinery: The Unfocused Aspects

Amylin Proteins and Pancreatic β-Cell Function

β-Cells are the most extensively studied pancreatic cells for their roles in glucose homeostasis in T2DM. Islet amyloid PP (amylin) is a β-cell peptide hormone that is secreted along with insulin in the ratio of approximately 100:1. Its secretion is also altered in diabetic patients. Amylin functions as an inhibitor of glucagon secretion and delays gastric emptying thus acting as a satiety agent [5]. Amylin action is executed through an area postrema (glucose-sensitive part of the brain stem) that collectively aims to reduce the demand of total insulin [6]. Besides these functions, amylin also plays roles in the destruction of β-cell via the formation of amyloid aggregates and fibers [7]. Findings from histopathology have shown the accumulation of extracellular amyloid proteins, hyperphosphorylated tau, ubiquitin, apolipoprotein E, apolipoprotein (a), c-Jun N-terminal kinases (JNK1), and islet-brain 1/JNK1 interacting protein-1 (IB1/JIP-1) as the characteristic feature of pancreatic islets in T2DM individuals, suggesting that amylin in association with endocrine system plays important roles in physiology, pathology, and progression of T2DM [8].

α-Cells

α-cells are known to play crucial roles in the pathophysiology of T2DM. The secretion of glucagon from α-cell is regulated by glucose, hormones, and other substrates that work in unison. Any abnormality in α-cells is reflected in altered glucose homeostasis [9]. In T2DM, a relative elevated secretion of glucagon takes place in fasting and postprandial states during normal and increased glucose levels along with altered hypoglycemic response [10]. According to the bi-hormonal hypothesis, T2DM is the consequence of insulin resistance/deficiency with a relative excess glucagon secretion, leading to a rate of hepatic glucose production that is much higher than the rates of glucose utilization. This consequently results in hyperglycemia. The hypothesis is supported by a plethora of clinical and experimental investigations [11, 12]. Reduced suppression of glucagon release under hyperglycemic conditions is a contributing factor to postprandial hyperglycemia [13]. Interestingly, α-cells do not show this behavior in the presence of adequate insulin levels, suggesting that impairment in insulin machinery also cause the abnormalities in glucagon release in T2DM [14]. In addition to this, hypoglycemia is remarkably influenced by glucagon secretion in T2DM patients treated with insulin. In such patients, the secretory response of α-cells to low-glucose concentrations is compromised, which further aggravates the risks of severe hypoglycemia [15]. The deficiency of glucagon action in response to hypoglycemia is linked with multiple failures in α-cell regulation [16]. Even in the situation of islet allotransplantation that helps diabetes patients to remain independent to insulin for a long time, the retarded response of α-cell response to hypoglycemia usually remains unaffected, indicating that the procedure does not completely restore the physiological functions of α-cells [17]. Collectively, defects in α-cell regulation and glucagon secretion lead to defective glucose sensing, loss of β-cell function, and insulin resistance.

δ-Cells, SsT, and Pancreatic PP Cells (F-Cells)

The δ-cells are located in the stomach, intestine, neuroendocrine cells, and pancreas. They secrete SsT in a pulsatile manner in response to fluctuations in glucose levels [18]. SsT regulates the endocrine functions and also plays an important role in the gut-brain axis. The receptors of SsT are present on α- and β-cells where they act as inhibitory receptors for the secretion of insulin and glucagon. SsT exerts a tonic inhibitory effect on the secretion of insulin and glucagon and facilitates the islet response to cholinergic activation. In addition, SsT is also involved in the suppression of nutrient-induced glucagon secretion [19]. Further, SsT significantly alters the normal glucose homeostasis and feedback loops [20].

F-cells of the pancreas release pancreatic PP after the food intake. It exerts inhibitory postprandial effects on gastric emptying, intestinal motility, exocrine pancreatic secretion, hepatic glucose production, and gallbladder contraction. Functional abilities of PP significantly affect food intake and energy metabolism [21]. When administered through intracerebroventricular route, PP exerts an orexigenic (appetite stimulating) effect in the brain. On contrary, intraperitoneal administration of PP reduces the food intake and lowers body weight by enhancing energy expenditure [22, 23]. Increased plasma levels of PP are implicated in obesity and diabetes.

Adipose Tissue and Resistin

Adipose tissue consists of adipocytes, connective tissue matrix, nerve tissue, stromovascular cells, and immune cells. The role of adipose tissue as an endocrine organ is well established [24]. It releases leptin, cytokines, adiponectin, complement components, plasminogen activator inhibitor-1, proteins of the renin-angiotensin system, and resistin. Apart from secreting factors/hormones, adipose tissue also functions in coordination with other hormone systems and the central nervous system. Typically, adipose tissues serve as a store house for fat under normal conditions, while they also release free fatty acids (FFAs) in metabolic disorders. Consistent decline in the function of β-cell in normal individuals has been shown to be associated with progressive secretion of FFAs and insulin resistance in adipose tissue [25]. Resistin or adipose tissue-specific secretory factor released from adipose tissue is largely implicated in the progression and development of T2DM [24]. It acts as an inhibitory hormone that causes resistance to insulin [26]. Levels of circulating resistin increase in T2DM, resulting in oxidative stress, insulin resistance, and platelet activation [27]. Expression of the resistin gene is also observed in the pancreatic islets, pituitary, and hypothalamus [28]. Although resistin is primarily secreted by macrophages in humans [29] where it is involved in the recruitment of immune cells and proinflammatory factors, the involvement of resistin is also seen in hyperglycemia and insulin resistance [30, 31]. Resistin-induced hyperglycemia and obesity are induced through the activation of AMP-protein kinase and decreased expression of gluconeogenic enzymes in the liver. Induction of insulin resistance is also evident in rodents after the administration of recombinant resistin that reverses with the immune neutralization [32].

Genetics

T2DM is notorious for being "the geneticist's nightmare." Occurring due to the combined contribution of genetic and environmental factors, leading to multiple gene alterations [33]. Multiple mechanisms act either directly or in association with other factors to influence the development and progression of T2DM. These include defects in pancreatic angiogenesis, innervation, and modification of parental imprinting [34]. The pathogenesis of T2DM depends on the intensity of both maternal and paternal insulin resistivity and/or insulin sensitivity [35]. According to one study, the first-degree relatives of T2DM patients live at a higher risk of developing T2DM and have a strong genetic predisposition to β-cell failure [36]. Moreover, β-cell dysfunction, autosomal dominance, and heterozygous mutations in β-cell transcription factors are some of the major causes leading to early onset of T2DM. The identified genes responsible for the early-onset T2DM include insulin promoter factor-1, hepatocyte nuclear factor (HNF)-4α, NeuroD1/BETA2, HNF-1α, and HNF-1β [37]. A hyperglycemic intrauterine environment has also been implicated in T2DM or pre-diabetes in the offspring of women suffering from gestational diabetes [38]. Also, during gestational diabetes, the expression of insulin receptor-β, PI3K (phosphatidylinositol 3-kinase) with its subunit p85α and GLUT-4 decreases with a compensatory elevation in the expression of GLUT-1 mRNA in placental tissues [39]. Polymorphism in resistin gene 299 (G>A) and increase in serum resistin is also known to be a contributing factor to increased insulin resistance with a subsequent higher risk of T2DM in offspring. Moreover, offspring carrying AA and combined GA + AA genotypes tend to be at higher risk [40]. On the other hand, diabetes also has the capacity to make genetic alterations leading to associated comorbidities. For instance, alterations in genes involved in vitamin synthesis leads to lowering of levels of riboflavin and glycemia, microalbumineria, and altered levels of uric acid in T2DM individuals and devel-

opment of insulin resistance due to vitamin D deficiency [41–46]. Importantly, the genes of vitamin D receptor and its binding protein along with CYP1α show polymorphisms in diabetics [42–44].

Gut

The gut serves as a prominent link between the brain and the enteric nervous system [47]. The secretion of gastrointestinal hormones (incretin, glucagon-like peptide-1 [GLP-1], and glucose-dependent insulinotropic polypeptide [GIP]) increases after food intake. These hormones assist insulin and glucagon in maintaining glucose homeostasis and improve α-cell glucose sensing. GLP-1 promotes assimilation of ingested nutrients through glucose-stimulated insulin secretion and evidently improves β-cell sensitivity to glucose [48]. Moreover, GLP-1 also suppresses glucose-dependent glucagon secretion, retards gastric emptying, and promotes satiety [49]. In the pancreas, β-cell proliferation and inhibition of apoptosis are promoted by GIP and GLP-1 that ultimately expand pancreatic β-cell mass. In addition, fat deposition is also facilitated by GIP. In the brain, GIP and GLP-1 are involved in appetite control. GIP also decreases gastric acid secretion, while GLP-1 decreases the duration of gastric emptying. Moreover, the insulinotropic effects of GIP and GLP-1 differ in T2DM patients such that GLP-1 secretion is impaired, while the secretion of GIP remains unaffected [50]. Alterations in incretin functioning and the associated pathways result in increased gastrointestinal permeability in T2DM and form one of the basic underlying mechanisms responsible for diabetic comorbidities in the latter phase [48, 49, 51].

The gut also releases other hormones which are involved in multiple signaling cascades. These include (but not limited to) ghrelin, galanin, cholecystokinin (CCK or pancreozymin) and leptin [52]. The enteroendocrine cells (I cells of the duodenum and jejunum) and neurons synthesize and release CCK in response to meals and induce pancreatic acinar cells to secrete pancreatic digestive enzymes. CCK also reduces gastric emptying and enhances the digestion process [53]. Vagus stimulation causes trypsin release from pancreas that hydrolyzes CCK to maintain homeostasis through the feedback mechanism. CCK is positively associated with leptin and insulin levels resulting in disrupted glucose homeostasis and diabetic complications in T2DM [53, 54].

Gut Microbiota

Diabetes is considered as a disease of the intestine where gut microbiota plays a crucial role [55, 56]. The concentration of microflora distally increases along the length of the gastrointestinal tract [57]. The flora of the upper intestine generally accounts for $<10^5$ cfu/mL of the total microflora content. The concentration of microflora increases in the mid-ileum to 10^7 cfu/mL and ultimately populates the colon heavily [57, 58]. Commonly populating bacteria in humans are (a) *Firmicutes* (60–80%): *Ruminiococcus*, *Clostridium*, and *Lactobacillus*; (b) *Bacteroidetes* (20–30%): *Bacteroides*, *Prevotella*, and *Xylanibacter*; (c) *Actinobacteria* (<10%): *Bifidobacterium*; (d) *Proteobacteria* (<1%): *Escherichia* and *Enterobacteriaceae*; and (e) yeast *Saccharomyces boulardi* [59]. Obesity/adiposity is undoubtedly a pivotal contributing factor in T2DM. Interestingly, the level of *Staphylococcus*, *Enterobacteriaceae*, *Faecalibacterium prausnitzii*, and *E. coli* increases during obese conditions, while *Bacteroides* concentration decreases [60]. Moreover, in T2DM, *Firmicutes*, *Lactobacillus gasseri*, *Streptococcus mutans*, and *E. coli* are increased, while proteobacteria, butyrate-producing bacteria, *Bacteroidetes*, *Roseburia*, *Eubacterium halii*, and *Faecalibacterium prauznitzii* are decreased considerably [59]. Changes in gut microbiota/gut-brain microbiota result in insulin resistance and disease/metabolic syndrome [59, 61]. Also, low-grade inflammation is remarkably influenced by obesity in association with alteration of gut-brain-microbiota interactions that render T2DM as an inflammatory disorder [62]. An increased intestinal permeability due to inflammation is evident in obesity and diabetes that may reach to leak gut conditions to facilitate the entry of gut microbes into circulation. This increases circulating LPS and thereby activates inflammasome formation [63]. Moreover, vagal control is significantly compromised in diabetes in association with chronic hyperglycemia, damaged interstitial cells of Cajal and gastroparesis (5–12% diabetic patients) [64]. Increase in mucosal surface area, intestinal weight, and number of goblet cells per villus leads to disrupted esophagus peristalsis and lower sphincter tone [65]. The overall disturbances in intestinal motor functions lead to stasis and bacterial outgrowth; thus, possibly disturbing the intestinal barrier and affecting permeability to allow the entry of microbes [63–65]. Moreover, circulating LPS are involved in the insulin resistance and diabetes progression toward comorbidities [63, 65, 66]. Gut microbes influence the metabolic and immune networks of the host to cause obesity and diabetes through enhanced nutrient absorption from the diet, cellular uptake of circulating triglycerides, prolonged intestinal transit time, altered bile acid enterohepatic cycle, enhanced de novo lipogenesis, reduced FFA oxidation, altered tissue composition of bi-

ologically active polyunsaturated fatty acid, chronic low-grade inflammation triggered by the endotoxin TLR-4 axis, and altered intestinal barrier function [67].

Lifestyle Modifications, Environmental Factors, and Management of T2DM

The pharmacological approach to treat T2DM can be only partly effective in the long-term management of diabetes. Major modifications in the lifestyle of patients along with the interventions through pharmacological approaches are crucial to ensure an effective management of the disease. These include changes in physical activity, dietary modifications, management of stress or associated factors, and improved sleeping patterns. The next few sections of this review will discuss and explore the potential of these factors in the management of diabetes when followed in parallel with the pharmacological management of the disease.

Physical Activity

Physical activity is positively associated with controlled glycemic levels among T2DM patients. Moderate but daily physical activity has been found to be an effective way to control the long-term manifestations of diabetes. These include walking, gardening, and performing common household chores. Walking is the most effective physical activity in T2DM, as it allows significant glycemic control with limited physical burden in patients who are already physically weak [68]. Moreover, a much warranted lifestyle alteration in T2DM patients are changes in sedentary patterns. Sedentary behavior leads to considerably low expenditure of energy. An extended sedentary period in T2DM patients is also associated with uncontrolled glycemic levels. A reduced sedentary time, therefore, is crucial in diabetes patients, which can be achieved by increasing the physical work [69]. In addition, regular aerobic exercise is acknowledged to improve HbA1c levels in patients with diabetes [70]. Aerobic exercise tends to improve health outcomes in patients through multiple mechanisms that include the manifold increase in mitochondrial densities, improved sensitivity to insulin, improved compliance of blood vessels, and lung functions with enhanced cardiac output [71].

Dietary Changes and Medical Nutrition Therapy

Insulin resistance and subsequent appearance of T2DM are closely linked with high intake of sugars, fried food, and red meat [72]. On the contrary, reduced risk of T2DM development is observed in case of intake of vegetables having high content of antioxidants, fiber, and other nutrients [73, 74]. The average energy intake of diabetes patients differs with their obesity status. Usually, for a non-obese diabetic patient, an average energy intake of 1,500–2,500 calories per day is recommended, while for obese patients, the average calorie intake is reduced to 800–1,500 calories per day. Limited intake of refined sugars is highly recommended in T2DM patients. Non-nutritive sweeteners (aspartame, saccharine, etc.) can be the good substitutes for sugar in such patients. Moreover, the restricted intake of food rich in saturated fats and cholesterol and its replacement with food rich in polysaturated fats is also recommended. In addition, changes in eating patterns, such as dividing meals into small fractions over the day rather than taking 1 or 2 large meals can prevent vigorous postprandial peaks in blood glucose levels [75]. Strict adherence to controlled diet with sufficient physical activity is largely associated with lower incidence of diabetes [76]. Incorporation of Paleolithic diet (a diet rich in lean meat, fish, fruits, and vegetables) in the daily routine of diabetic patients results in marked improvement in glucose handling [77]. The employment of nutritional therapy in the management of diabetes is also widely suggested. Nutritional therapy is an approach to treat a disease through the modifications in food and nutrition intake. The application of evidence-based nutrition care therapy in diseased patients by a qualified and registered dietician is termed as medical nutrition therapy [78]. Reduced reliance on oral hypoglycemic therapy is evident in diabetes patients receiving nutritional therapy [79]. Also, considerable improvements in clinical outcomes are observed in diabetes patients receiving intensive nutritional education by registered dietician in comparison to patients receiving basic nutrition information (BE) [80]. Taken together, simple but profound changes in dietary pattern in diabetic patients is a potential approach to curb the long-term implications of diabetes. Moreover, successful application of nutritional therapy in individuals with diabetic conditions can be a lucrative approach to achieve a better management of diabetes with improved health outcomes.

Stress

Increased levels of stress are associated with poor treatment adherence and glycemic control in T2DM patients [81]. In a longitudinal study, moderate/high levels of stress were found to be accountable for multifold increase in the incidences of diabetes [82]. Moreover, consistent exposure to stressors, compromised mental health, and psychological stress are highly implicated in increasing

risk of T2DM development [83]. Allostatic load (wear and tear in the body occurring as a result of chronic exposure to psychological stress) is assumed to be the major factor responsible for this increased risk of T2DM in such individuals [84]. In addition, consistent stress is also implicated in worsening of clinical outcomes in T2DM patients. Chronic stress is associated with dysregulated glucose metabolism and neuroendocrine function accompanied with low-grade inflammation. A majority of factors that are implicated in T2DM are largely influenced by psychological stress including the release of glucose (and lipids) in circulation, expression of inflammatory cytokines, and elevated blood pressure [85]. In one study, in type 2 diabetes patients when exposed to acute stress during the postprandial period, considerable increases in blood glucose levels were observed [86]. Apparently, treatment strategies, including stress management interventions, are a promising approach in effectively preventing or controlling the incidence of type 2 diabetes.

Sleep Patterns and Chronopharmacology

Although physical activity and maintained dietary pattern result in considerable improvements in the management of T2DM, they cannot be envisioned as the sole contributors to the worsening of diabetes incidences. Sleep is another modifiable lifestyle behavior that has proven roles in influencing metabolic health and energy status. Optimization of sleeping patterns is crucial in diabetes control [87]. A population-based study suggests that short sleep (<5 h) or insomnia is associated with increased risk of T2DM [88]. In similar studies, poor sleep was associated with higher HbA1c levels (>7%) and insulin resistance in T2DM patients [88]. Disturbed circadian rhythms and sleep-wake patterns also result in significant effect on onset, development, and management of diabetes [89]. Shift workers tend to remain much prone to metabolic disorders due to consistent sleep loss and disrupted circadian rhythm [90]. In addition, developed propensity of napping as a consequence of poor or insufficient nocturnal sleep is also associated with high risk of T2DM [91]. In one study, experimental manipulation of sleep and circadian pattern resulted in significant reduction in insulin response to standardized meal which could be recovered with restored sleeping patterns [92]. Changes in hormones that regulate appetite (leptin and ghrelin) are observed to be associated with short sleep causing an increased urge for carbohydrate-rich food and increased calorie intake [89, 93]. Moreover, lack of sleep also results in oxidative stress and release of orexin or hypocretin, a neuropeptide that regulates sleep and appetite and causes the stimulation of sympathetic nervous system and increased release of cortisol with simultaneous decrease in growth hormone secretion, all leading to considerable hyperglycemia [89, 94].

Pharmacokinetics and pharmacodynamics (PK-PD) are markedly influenced by daily rhythms in physiology. This phenomenon is termed chronopharmacology [95]. Indeed, the pathogenesis of diabetes largely depends on hormonal and body homeostasis. Chronopharmacology should be considered as part of treatment strategies for diabetes. The failing β-cells in T2DM do not lose all their capability to respond to glucose. Insulin secretion in response to stimulation through amino acids or other hormones such as glucagon-like peptide 1 (GLP-1), remains preserved [96]. The levels of leptin (satiety hormone) in blood generally remain higher between midnight and early morning, conceivably to suppress appetite during the night [97]. Moreover, the levels of ghrelin increase with increase in the duration of sleep [93]. In addition, the time dependency in GLUT4-mediated glucose uptake is also a function of circadian variation [98]. Furthermore, meal timings can modify the diurnal rhythm of blood leptin levels [99]. Both ghrelin and leptin work with other hormones and HPA axis through feedback loops to indirectly affect the psychophysiological satisfaction in diabetic patients [100]. Chronopharmacology, therefore, may considerably affect diabetic pathophysiology and PK-PD of administered drugs.

Interplay of Genetics, Gut Microbiota, Lifestyle, and Environmental Factors

Multiple epidemiological investigations have suggested that the effects of multiple T2DM-associated loci can be attenuated by improving lifestyle, dietary patterns, and other associated environmental factors. For instance, the Ala12 variant of PPARγ is associated with improved insulin sensitivity. Apparently, the Ala12 carriers are more responsive to unsaturated fat and less responsive to saturated fat. On contrary, the Pro12 variant carriers of PPARγ are more responsive to the deleterious effects of saturated fat and altered glucose homeostasis. Seemingly, unsaturated fat interacts with PPARγ Ala12 variant and upregulates the activity of latter [101]. Potential gene-environment (G × E) interactions also occur between TCF7L2 risk-variant (rs7903146) and lifestyle modifications (physical activity, MNT, and dietary changes). Decreased insulin resistance and reduced risk in TCF7L2 risk-variant carriers is significantly affected by lifestyle modifications

[102, 103]. A common SNP in fat mass and obesity associated gene (FTO rs9939609) is associated with increased risk of T2DM. Increased physical activity reduces the FTO rs9939609-induced obesity and associated risk of T2DM [104]. SNP in glucokinase regulatory protein gene results in an insulin-raising allele, GCKRrs780094. Its interaction with the whole grain (increased whole grain intake) results in reduced fasting insulin in the carriers [105]. The potassium voltage-gated channel subfamily Q member 1 (KCNQ1) is a susceptible gene in T2DM. Mutations in KCNQ1 are associated with decreased insulin secretion. Reduced expression of noncoding RNA Kcnq1ot1 in Kcnq1 genetic region leads to increase in cyclin-dependent kinase inhibitor 1C (Cdkn1c) expression, resulting in reduced pancreatic β-cell mass and insulin release. The CCAAT sequence in the promoter region of Cdkn1c gene serves as the binding site for transcription factor C/EBP that increases the further expression of Cdkn1c. Evidently, the expression of C/EBPβ results in endoplasmic reticulum stress to cause dysfunctions in β-cells. The accumulation of C/EBPβ in pancreatic β-cells increases in the presence of high fat diet, thereby potentiating the β-cells dysfunction in the vulnerable population [106]. Collectively, the emerging investigations to explore the interactions between gene and environmental factors suggest a high influence of dietary patterns, physical exercise, and other lifestyle interventions on the expression of genes that are peculiar to the development of T2DM.

Apart from gene expression, environmental factors also tend to exert a potential impact on gut microbiota. The gut environment is affected by a number of factors including the diet, pH, and nutrient absorption. While the presence of Firmicutes and Proteobacteria increases under the influence of carbohydrates and simple sugar-rich diet, saturated fats, and animal protein-rich diet encourages the proliferation of Bacteroidetes and Actinobacteria [107]. Moreover, a high -at diet is also accountable for significant alterations in intestinal flora, including the *Bifidobacterium* and *Bacteroides* (increased Gram-negative/Gram-positive bacteria ratio). This allowed and increased secretion of LPS, fat content, body weight, and inflammatory reactions associated with T2DM [108]. Reduction in butyrate is largely responsible for the loss of tight intestinal barrier. An intestinal pH of 5.5 favors the proliferation of butyrate-producing *Phytophthora* which starts to diminish with a pH value of 6.5 [109]. In addition, the hypoglycemic agents utilized for the antidiabetic therapy also pose a remarkable influence on the gut microbiota. Metformin and acarbose are known to increase the proliferation of lactobacilli, Akkermansia, and several other bacteria that are acknowledged to exert beneficial effects in diabetes [110].

Gut microbiota composition also affects the regulation of expression of different genes in T2DM. Although reports are limited in terms of potential interactions between gut microbes and T2DM associated gene variants, existing reports on the influence of gut microbes in the expression genes that are crucial in T2DM are highly suggestive of a complex gene-microbes interplay in the etiology of T2DM. Also, microbiome plays a crucial role in the epigenetic regulation of genes by the modification of DNA methylation [111]. *F. prausnitzii*, a short-chain fatty acid-producing bacteria was found crucial in epigenetic regulation of FFA receptor gene in patients of T2DM. A significant reduced presence of *F. prausnitzii* was evident in such patients. As a result, a considerably low methylation in the promoter region of FFA receptor gene is observed in these individuals [112]. Increased release of pro-inflammatory cytokines is a key event in T2DM. Microbes are largely known to be associated with increased release of inflammatory cytokines by producing the products such as LPS that promote low-grade inflammation and endotoxemia. On contrary, several microbes are known to induce the expression of anti-inflammatory cytokines, including the IL-10 and IL-22, that have proven roles in improving the insulin sensitivity *Roseburia intestinalis*, *Bacteroides fragilis*, *Akkermansia muciniphila*, *Lactobacillus plantarum*, and *Lactobacillus casei* [113]. Two other beneficial microbes – *Bacteroides vulgatus* and *Bacteroides dorei* – are observed to increase the expression of tight junction genes in T2DM to compensate with the compromised gut permeability (leaky gut) [114]. A major contribution of probiotics is observed in the case of glucose metabolism and homeostasis. For instance, *L. gasseri* BNR17 is known to increase the expression of GLUT-4 transporter gene [115]. Another gut microbe, *L. casei* is witnessed to increase the expression of multiple T2DM-related genes, including ClC1-7, GlyRα1, SLC26A3, SLC26A6, GABAAα1, Bestrophin-3, and CFTR, thus resulting in a significant reduction in hyperglycemia [116]. It appears to be of vital importance to consider the potential interplay between various T2DM-related genes and these microbes. Undoubtedly, the absence of these microbes among the gut microbiota can be largely responsible for the altered regulation of different genes in T2DM patients. Also, exploring the interactions between different T2DM-associated gene variants and gut microbiota is warranted to further understand the complex interactions between environmental factors, gut microbiota, and genetics in the development of T2DM.

Table 1. Multiple targets of different phytoconstituents in the management of T2DM and their possible outcomes [133–140]

Phytoconstituents	Mode of action/targets	Outcomes
Curcumin	↓ TNF-α, ↓ NFkB activation, ↓ lipid peroxidation, ↓ lysozyme enzyme activity, and ↑ PPAR-γ activation	Increased insulin sensitivity, decreased glucose intolerance, and hypoglycemia [133]
Rutin	↓ G6Pase and glycogen phosphorylase activity, ↑ hepatic hexokinase activity, and ↑ PPARγ activation	↓ Hepatic glucose production, ↑ glucose tolerance, and improved insulin sensitivity [134]
Resveratrol	SIRT1 activation, ↓ oxidative stress, and ↑ GLUT4 translocation through AMPK/Akt/iNOS signaling pathway	Improved insulin signaling, ↑ glucose-mediated insulin secretion, and ↓ loss of β cells [135]
Quercetin	↑ GLUT4 translocation through AMPK signaling, ↓ G6Pase, and ERK1/2 activation	↑ Glucose uptake, ↓ hepatic glucose production, glucose-induced insulin secretion, and improves β-cell function [135, 136]
Genistein	↑ Hepatic hexokinase activity, and ↓ cytosolic PEPCK	Improved lipid and glucose metabolism and reduced fasting glucose [137]
Hesperidin	↑ GLUT4 expression, ↓ TNF-α, and IL-6 expression, ↑ antioxidants	↑ Glucose uptake, ↓ HbA1c, and ↓ oxidative stress [138]
Naringin	↑ G6Pase activity, ↑ insulin receptor and GLUT4 expression, and ↑ antioxidants	↓ Hepatic glucose production, ↑ glucose uptake, and ↓ oxidative stress [138]
Naringenin	↑ Expression of GLUT4 and PPARγ	↑ Glucose uptake, decreased glucose intolerance, and reduced blood glucose levels [139]
Vitamins A, D, and E	↑ PPARβ/δ expression, ↑ RAR expression, ↑ DNA tail length of liver and pancreas, and ↓ G6Pase, ↓ β-cell apoptosis	Decreased glucose intolerance, ↑ β-cell mass, ↓ hepatic glucose, and ↓ hyperglycemia [135]
Fisetin	↓ G6Pase and ↓ cytosolic PEPCK	↓ Hepatic glucose and improved lipid and glucose metabolism [140]

T2DM, type 2 diabetes mellitus; G6Pase, glucose-6-phosphatase; PEPCK, phosphoenolpyruvate carboxykinase.

Current Approaches for Diabetes Management: What Are We Missing?

The guidelines for the pharmacological management of diabetes provided by American Diabetes Association suggest that metformin be prescribed as the initial intervention to T2DM patients. However, the same guideline also indicates that vitamin B_{12} deficiency is a prominent side effect observed in metformin consumers and a periodic vitamin B_{12} measurement is required in such patients [117, 118]. Furthermore, metformin is also notorious for causing lactic acidosis, especially in patients with kidney disease, liver injury, or other CVS complications that create a low level of oxygen in circulation [119]. For T2DM patients with cardiovascular or CKDs, the guidelines recommend adding sodium-glucose cotransporter 2 (SGTL2) inhibitors and/or glucagon-like peptide 1 receptor agonists along with hypoglycemic agents [118]. The employability of SGTL2 inhibitors with almost all classes of hypoglycemic agents makes them ideal candidates to be combined when dual and triple combination therapies are warranted [120]. In an ideal scenario, a drug used in combination should be able to reverse the pathology with an improved overall health status of the patient and ensure that no new complications arise due to the existing management strategies. In case of T2DM, drug combination should not only be able to just merely reduce the glycosylated hemoglobin levels (HbA1C) but also an improved overall metabolic condition of the patient is expected through such interventions [120]. The combination of SGTL2 inhibitors with metformin may have proved beneficial in curbing hyperglycemia that cannot be controlled by metformin alone [120], but the adverse effects associated with the SGTL2 inhibitors still remain unresolved. Genital infections caused by SGTL2 inhibitors due to high glycosuria still remain an unfocussed aspect while prescribing such combinations. In addition, during the event of excessive osmotic diuresis caused by SGTL2 inhibitors, a low extracellular fluid volume and subsequent hypotension is another complication that may arise [121]. Multiple reports have also raised concerns regarding the use of SGTL2 inhibitors in diabetes due to their substantial involvement in causing diabetic ketoacidosis [122]. Two separate reports published in 2015 claimed

that canagliflozin, an SGTL2 inhibitor is implicated in pancreatitis in T2DM patients [123, 124]. GLP-1 agonists are also a preferred class of adjuvant hypoglycemic agents that are combined with first-line hypoglycemics [125]. Apart from gastrointestinal disorders (nausea, vomiting, and constipation), infections and acute renal injury, a major raising concern regarding the use of GLP-1 agonists is their association with pancreatitis [125, 126]. Cases of acute pancreatitis are reported with the use of liraglutide and exenatide [127, 128]. More importantly, recent reports also raise concerns regarding the long-term reliance on incretin-based therapies due to frequently reported cases of their association with pancreatitis and pancreatic cancer [129]. Studies based on FDA Adverse Events Reporting System demonstrated that incretin-based therapies are associated with the increased incidences of pancreatic and thyroid cancer [130, 131]. Exenatide use is also positively associated with the incidences of bone fractures [132].

Alternatives: Phytoconstituents

Failure of monotherapy in diabetes is simply managed by the dual or triple drug combination therapies that involve the addition of supportive hypoglycemic agents with the first-line drugs. However, adding the supportive or second-line drugs in combination seldom includes the assessment of risk factors associated with these new additions. The sole aim of these therapies remains to be a controlled glycemic condition. Unfortunately, in the pursuit of maintaining normal blood glucose levels, the occurrence of new complications is largely taken for granted. Monotherapies supplemented with herbal extracts or phytoconstituents have showed appreciable improvements in the blood glucose levels in diabetic patients. Chemical constituents from plants have also proved to be promising alternatives. Table 1 represents the known effects of different phytoconstituents in diabetes exerted through multiple targets. As a result, unlike in the case of conventional single target therapy where chances of treatment failures are high, therapy failures with multi-targeting approach are rare.

Conclusions

Diabetes is a metabolic disorder that is influenced by a variety of factors. Recent insights into the pathogenesis of diabetes have unraveled newer pathways and factors that contribute substantially in disease development and progression. Insulin resistance and β-cell dysfunction are the 2 major events that are largely responsible for the onset of diabetes. A major objective of this review is to focus on the unfocused aspects of diabetes to develop better strategies for diabetes treatment. In this review, we have discussed the factors that have played crucial roles in the etiology of T2DM but have not received adequate attention. We have also discussed the efficiency of existing approaches in the treatment of T2DM. Lifestyle modifications that favor the improvement of management of diabetes and their complex interplays with genetics and gut environment is a crucial factor that warrants further research in the development of more efficient and individualized therapy approaches for disease treatment. The use of multidrug combination therapy in diabetes may have improved health outcomes in T2DM patients and also result in additional complications that need serious consideration. Moreover, more attention is required toward the developing comorbidities during diabetes. The diabetic milieu accelerates the formation of advanced glycation end products that may encourage the development of diabetic complications and even cancer in diabetic patients. Multiple pathways are involved in diabetes that can contribute to the manifestation of comorbidities that are largely neglected during disease treatment.

Multitargeting is a promising approach for the treatment of T2DM as it includes multiple pathways. The failure of single target approaches is the major challenge faced in T2DM treatment. Phytoconstituents are promising as they interact with multiple pathways simultaneously. However, the reluctance to rely on phytoconstituents as the main therapy still remains as a limiting factor for such drugs to serve as mainstream interventions.

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Conflict of Interest Statement

All authors have read the journal's policy on disclosure of potential conflicts of interest and have none to declare.

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