Chapter

Medicinal Plants, Bioactive Compounds, and Dietary Therapies for Treating Type 1 and Type 2 Diabetes Mellitus

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Abstract

Medicinal plants, bioactive compounds, and dietary measures have been found to be effective in the treatment of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). About 463 million people have diabetes worldwide; estimates project 700 million people by 2045. While T1DM is caused by the loss of beta cells of pancreatic islets that produce insulin, resulting in the deficiency of insulin, T2DM, which constitutes over 90 to 95% of all DM cases, is caused by insulin resistance, and could relatively combine reduction in the secretion of insulin. *Aloe vera, Terminalia chebula, Perilla frutescens, Curcuma longa, Zingiber zerumbet, Nigella sativa, Gongronema latifolium, Pachira aquatic, Caesalpinioideae, Azadirachta indica, Artemisia dracunculus, Artemisia herbaalba, Vachellia nilotica, Abelmoschus moschatus, Cinnamomum verum, Salvia officinalis, Tinospora cordifoli, Pterocarpus, Ocimum tenuiflorum, Mangifera indica, Syzygium cumini, Coccinia grandis, Caesalpinia bonduc, Gymnema sylvestre, Carthamus tinctorius, Allium sativum,* and *Trigonella foenum-graecum* are among the medicinal plants shown to be effective in controlling and treating T1DM and T2DM. Bioactive compounds such as lycopene, vitamin E, vitamin D, genistein, quercetin, resveratrol, epigallocatechin-3-gallate, hesperidin, naringin, anthocyanin, etc. are useful in treating T1DM and T2DM.

Keywords: medicinal plants for treating diabetes type 1 and 2, bioactive compounds for treating diabetes type 1 and 2, dietary measures for managing diabetes, diabetes mellitus, herbal therapy for diabetes

1. Introduction

Diabetes mellitus (DM), simply called diabetes, are metabolic disorders characterized by varying or persistent hyperglycemia (high levels of sugar in the blood) over an extended time period. The most common symptoms of DM usually include increased appetite, increased thirst, and frequent urination. If not treated or when poorly managed, DM can result in several complications. While acute complications of DM often include hyperosmolar hyperglycemic state, diabetic ketoacidosis, or even death, severe chronic complications include cognitive impairment, damage to the eyes, damage to the nerves, foot ulcers, chronic kidney disease, stroke, and cardiovascular disease [1]. Diabetes mellitus (DM) manifest by hyperglycemia,

defects in insulin secretion, glucose intolerance, and/or failure of insulin activity to boost uptake of glucose. Diabetes mellitus (DM) causes global burden as a result of its high morbidity/mortality rates, as well as the capital intensity required for its treatment and management. About 463 million people have DM worldwide, while estimates project 700 million people by 2045 [2].

Globally, epidemiological studies showed that diabetes is more prevalent in middle- and low-income countries with about 50 percent of cases unreported and undiagnosed [2, 3]. Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are the most common types of DM. Over 90 to 95% of DM cases are T2DM [2, 4], while the remain 5 to 10% are other types of DM, including T1DM, the gestational diabetes, and other minor specific types rarely encountered. Worldwide, there has been serious search for cost effective and potent drug against T1DM and T2DM in order to reduce the annual death rate [5]. Various antidiabetic therapeutics and treatments that make use of conventional medications are often laborious as they are not single-dose treatment regimen; some are taken throughout lifetime. In recent years, medicinal plants, bioactive compounds, and dietary measures have been found to be effective in the treatment of T1DM and T2DM.

The increasing awareness of the safety and efficacies of medicinal plants, dietary therapy, and bioactive compounds in treatment of various metabolic diseases is gradually reshaping treatment measures for many metabolic diseases [6–8], including DM. Medicinal plants and their bioactive constituents play important role in regulating metabolisms in humans, usually resulting in improved health and general wellbeing. They can be largely found in fruits and vegetables, medicinal plants [9–16], whole grains [11], etc., and could be consumed every day. The health benefits of bioactive compounds are commonly reported in animal and cell studies, which often include regulating cell signaling pathway, scavenging free radicals, and decreasing inflammation [17, 18]. Natural materials containing bioactive compounds have been traditionally employed in the treatment of diabetes mellitus (DM). Due to their safety, availability, and tolerable side effects, bioactive compounds applications have been suggested for reducing incidences or delaying progression of many diseases, such as T1DM and T2DM, constipation, Alzheimer's disease, etc. [19, 20]. This chapter provides detailed descriptions and efficacies of the medicinal plants, bioactive compounds, and dietary nutrients shown to be effective in treating T1DM and T2DM. Although the medicinal plants, bioactive compounds, and dietary nutrients discussed in this chapter are mainly focused on T1DM and T2DM, they could also be effective against the less common types of DM such as the gestational diabetes and other minor specific types rarely encountered.

2. Causes and complications of T1DM and T2DM

Type 1 diabetes mellitus (T1DM) is caused by the loss of beta cells of pancreatic islets that produce insulin, resulting in the deficiency of insulin. T1DM can be additionally classified as idiopathic or immune-mediated. Most T1DM has the nature of the immune mediation, where an autoimmune attack mediated by T-cell results in loss of beta cells and consequently insulin [21]. The majority of the affected individuals are otherwise mostly healthy, with healthy weight during the onset occurrence. Responsiveness and sensitivity to insulin are often normal, particularly in initial stages. Though T1DM is often referred to as "juvenile diabetes" due because of the regular onset in children, most people with T1DM are currently adults. T1DM could be accompanied by unpredictable, irregular high levels of blood sugar, and potentials for serious low levels of blood sugar or diabetic ketoacidosis. Other T1DM complications are endocrinopathies (such as Addison's disease),

gastroparesis (that results in irregular dietary carbohydrates absorption), infection, and impairment in the counterregulatory responses to low levels of blood sugar. These usually occur in 1–2% of those with T1DM [22]. T1DM is in part hereditary, with several genes, such as some HLA genotypes, having influence on T1DM risks. In those with genetic susceptibility, the onset of DM could be caused by at least environmental factors, including diet, stress, or viral infection [23]. Although many viruses have been reported, however, no reliable evidence has supported their potentials to cause DM in humans [23, 24]. Among dietary factors, it has been reported that gliadin (a gluten protein) can be a factor in the development of T1DM, although the mechanism has not been established, at least not entirely. T1DM occurs at any stage of life; significant percentage has been detected in adulthood. Latent autoimmune diabetes of adults (LADA) is a term used when T1DM occurs in adulthood, and has slower onset than T1DM in children. Due to this difference, few people make use of the unofficial term "type 1.5 diabetes" in place of T1DM in adults. Adults with latent autoimmune diabetes of adults are often misdiagnosed as having T2DM initially, due to age instead of cause [25].

On the other hand, type 2 diabetes mellitus (T2DM), which constitutes over 90 to 95% of all DM cases, is caused by insulin resistance, and could combine relative reduction in the secretion of insulin. The defects in body tissues response to insulin is considered to be related the insulin receptors. Cases of DM with known defects are categorized separately. Many individuals with T2DM present clinical prediabetes evidence (such as impaired glucose tolerance and/or impaired fasting glucose) prior to developing T2DM [26]. Prediabetes progression to overt T2DM could be reversed or slowed by lifestyle medications/changes, which enhance sensitivity to insulin or decrease the production of glucose in the liver [27]. T2DM is mostly because of lifestyle and environmental factors, as well as genetics [28]. Some lifestyle factors result in T2DM development, such as obesity (body mass index ≥30), urbanization, stress, poor diet, and lack of physical activities. Dietary factors, including sugar-sweetened drinks, have been correlated with increased risks of T2DM. Fat types in the food are also significant; trans fats and saturated fat increase the risks, while monounsaturated and polyunsaturated fat reduce the risks [28]. Excessive consumption of carbohydrates dense foods such as white rice may increase risks of DM [29]. Lack or insufficient physical activities can increase risks of DM in some individuals. Adverse childhood experiences (ACEs), such as neglect, abuse, and household challenges, increase possibility of T2DM by 32% later in life, with neglect reported to have the most significant effects [30].

3. Medicinal plants for T1DM and T2DM treatment

Several medicinal plants have been shown to be effective in treating and managing DM. *Aloe vera, Terminalia chebula, Perilla frutescens, Symplocos, Symphytum, Cactaceae, Zingiber zerumbet, Chrysanthemum morifolium, Tinospora cordifolia (guduchi), Nigella sativa, Gongronema latifolium, Pachira aquatic, Caesalpinioideae, Azadirachta indica, Artemisia dracunculus, Artemisia herbaalba, Andrographis paniculata L, Asphodelaceae, Mentha, Fabaceae, Achyranthes, Vachellia nilotica, Abelmoschus moschatus, Cinnamomum verum, Panax, Salvia officinalis, Tinospora cordifoli, Pterocarpus, Ocimum tenuiflorum, Momordica charantia, Mangifera indica, Syzygium cumini, Coccinia grandis, Caesalpinia bonduc, Liriope, Sarcopoterium, Swertia, Combretum, Gymnema sylvestre, Bauhinia, Ferula assafoetida, Carthamus tinctorius, Allium sativum,* and *Trigonella foenum-graecum* are among the medicinal plants shown to be effective in controlling and treating T1DM and T2DM [31]. **Table 1** shows the list of plants known to be effective in treating T1DM and T2DM.

Scientific name of plant	Common name	Parts used	Effectiveness and mechanisms against T1DM and T2DM	Type of study	Reference
Allium sativum	Garlic	Bulb	Antihyperlipidemic and antihyperglycemic effects. Lowers FBG, improves glycemic control via increased secretion of insulin and improved sensitivity to insulin	In vivo	[32]
Aloe vera	Aloe vera	Leaves	Prevents changes in insulin levels. Diabetic kidney shows distinctive changes resulting in kidney failure or renal insufficiency. Major alteration was mostly reported in kidney tissue proximal tubules in diabetic animal models	In vitro	[33]
Bauhinia forficate	Brazilian orchid tree	Leaves	After treatment for 31 days using decoction, in T2DM group, urinary glucose and plasma glucose levels reduced significantly	In vitro	[31]
Caesalpinia Bonducella	Gray Nicker	Seeds	The 50% ethanolic and aqueous extracts of seeds of *Caesalpinia bonducella* had hypolipidemic and antihyperglycemic activities in streptozotocin-induced diabetic rats. Both ethanolic and aqueous extracts indicated potent hypoglycemic properties in chronic T2DM rats. The antihyperglycemic properties of the seed extracts could be because of the glucose absorption blockage	In vitro	[31]
Carthamus tinctorius	Safflower	Flower	The hydroalcoholic extracts from flower of *Carthamus tinctorius* can treat T1DM and T2DM. The flower of *Carthamus tinctorius* is rich in flavonoids, including kaempferol and quercetin, with hypoglycemic and antioxidant effects	In vivo	[34]
Cinnamomum verum	Cinnamon	Whole plant	*Cinnamomum verum* in diet reduces risks of cardiovascular diseases and DM. *Cinnamomum verum* reduced HbA1C (hemoglobin A1c) by 0.83% in comparison to the usual care alone, which reduced hemoglobin A1c by 0.37% in T2DM patients in a controlled, randomized trial	In vivo	[32]
Combretum Micranthum	Kinkeliba, geza'	Leaves	Hypoglycemic properties of *Combretum Micranthum* extracts were studied using fasting blood sugar and glucose tolerance in healthy rats. The aqueous extracts from leaf of *Combretum Micranthum* has antidiabetic properties against T1DM and T2DM	In vitro	[31, 35]
Ferula asafoetida	Asafoetida	Gum	With the presence of antioxidants, gum of *Ferula assafoetida* decrease the free radical levels in cells, and stimulates insulin secretion and synthesis in T2DM, and residual pancreatic cells hyperplasia and reduction of glucose level in blood	In vivo	[35]

Scientific name of plant	Common name	Parts used	Effectiveness and mechanisms against T1DM and T2DM	Type of study	Reference
Ginseng	Ginseng	Root, berries, stalk, leaves	Ginseng significantly reduced fasting blood glucose (FBG) and insulin resistance in patients with T2DM. Amongst 30 T2DM patients treated using Renshen tangtai (injection containing Ginseng polysaccharides and polypeptide), 86.7% presented significant effects on symptoms of T1DM and T2DM	In vivo and in vitro	[31, 32]
Gymnema sylvestre	Cowplant	Leaf	The crude extracts of *Gymnema sylvestre* and dihydroxy gymnemic triacetate (a compound obtained from *Gymnema sylvestre*) have hypoglycemic effects in streptozotocin-induced diabetic rats in time- and dose-dependent manners	In vitro	[35]
Liriope spicata	Monkey grass	Leaves	Aqueous extracts of *Liriope spicata* resulted in significant reduction in levels of fasting blood sugar and significantly improved glucose tolerance and insulin in streptozotocin-induced diabetic mice.	In vitro	[35]
Mangifera indica	Mango	Leaves	Extracts of mango leaves have hypoglycemic properties, possibly because of decrease in intestinal glucose absorption	In vitro	[31]
Momordica charantia	Bitter melon	Fruit	*Momordica charantia* reduced postprandial and fasting serum levels of glucose in patients with T2DM. Bitter melon showed antihyperglycemic effects by increasing the expression of glucose transporter type 4 (GLUT4), activating AMPK, inhibiting protein tyrosine phosphatase 1B (PTP1B), promoting beta cells recovery and insulin-mimicking action	In vivo	[32]
Sarcopoterium spinosum	S. spinosum	Root	*Sarcopoterium spinosum* root aqueous extracts induce antidiabetic effects on progressive hyperglycemia in mice with T1DM and T2DM. Aqueous root extracts of *Sarcopoterium spinosum* has insulin-like action in target tissues	In vitro	[35]
Swertia punicea	Swertia	Whole plant	Mechanism *Swertia punicea* hypoglycemic effects has been established by ameliorating insulin resistance in mice with T1DM and T2DM	In vitro	[35]
Trigonella foenum graecum	Fenugreek	Seed	Powdered fenugreek (15 g) administered to T2DM patients decreased Darqndkhvn sense	In vivo	[36]
Urtica dioica	Stinging nettle	Leaves	*Urtica dioica* leaves' aqueous extracts enhanced glycemia levels in rats with T2DM, and is mediated by essential effects on the pancreatic beta-cells functional status	In vivo	[37]

Scientific name of plant	Common name	Parts used	Effectiveness and mechanisms against T1DM and T2DM	Type of study	Reference
Zingiber zerumbet	Bitter ginger	Root	Ethanol extracts of bitter ginger rhizome were administered to streptozotocin-induced diabetic rats. After 3 months of diabetic conditions, weight gain in streptozotocin-induced diabetic rats was significantly less in comparison with healthy rats, while the glucose levels in the blood were significantly higher. Body weight reduction was unnoticeable in streptozotocin-induced diabetic rats receiving ethanol extracts of bitter ginger rhizome during study period	In vitro	[38]

Table 1.
Medicinal plants effective against T1DM and T2DM.

4. Bioactive compounds and dietary nutrients with effectiveness against T1DM and T2DM

Many dietary nutrients and bioactive compounds have effectiveness in the treatment of T1DM and T2DM. This section discusses the most common bioactive compounds and dietary nutrients for treating DM, with more focus on type 1 and type 2 DM. **Figure 1** shows the complex mechanisms of cell signaling targeted by T1DM and T2DM therapeutic strategies and bioactive compounds of plants.

4.1 Vitamins

Vitamins are bioactive organic compounds which are essential micronutrients organisms required in small quantities, usually within micrograms to milligrams, for the proper functioning of body metabolisms [39]. Here are some vitamins for treating T1DM and T2DM.

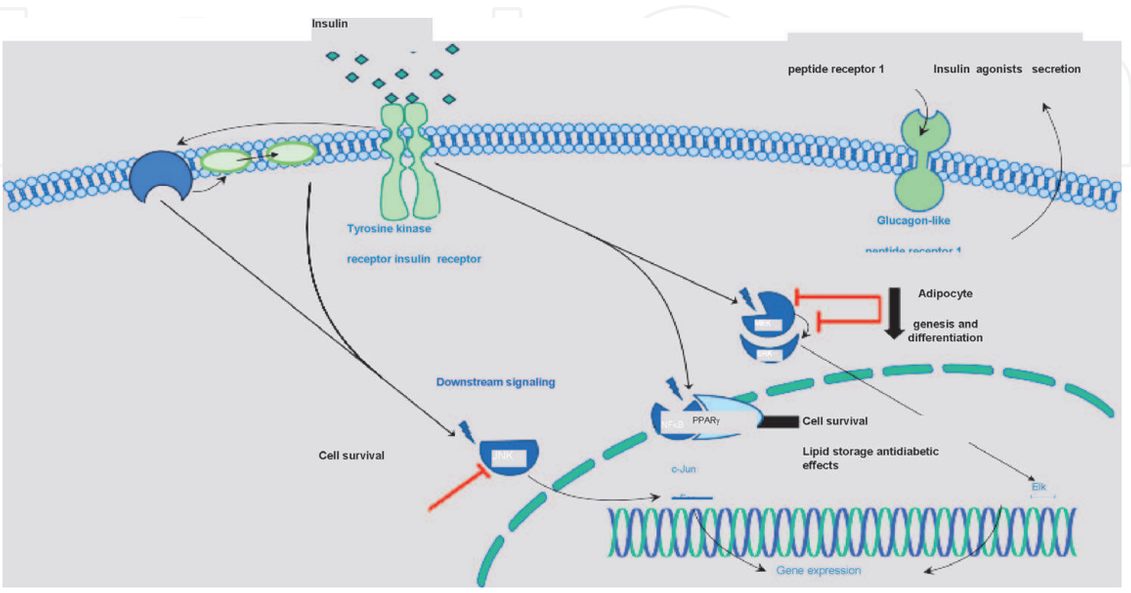

Figure 1.
Few complex mechanisms of cell signaling targeted by T1DM and T2DM therapeutic strategies and bioactive compounds of plants.

4.1.1 Vitamin A for T1DM and T2DM treatment

Vitamin A has been known to be important in treating DM. it is a group of unsaturated organic compounds essential to organisms, e.g. retinol, retinal, as well as many provitamin A carotenoids [39]. Retinol (or Vitamin A) is essential nutrient required for vision, normal growth, and reproduction. Retinoic acid (RA) is a metabolite of vitamin A with physiological importance. Retinol is converted intracellularly to 9-cis-retinoic acid or retinal all-trans-RA [40]. Mechanisms by which vitamin A influence T1DM and T2DM include adipose and obese biology regulation, increasing insulin sensitivity, β cells regeneration, and oxide radicals' chelation [40]. It has been reported that all-trans-retinoic acid may enhance insulin signaling through preventing the activity of protein kinase C (PKC) by binding to isozymes of PKC [40]. Protein kinase C was reportedly high in DM and blocked insulin signaling [40]. Retinoic acid increases secretion of insulin and levels of insulin mRNA in cultured islets, through raising pancreatic glucokinase by the glucokinase promoter activation. Retinol and retinoic acid are uncoupling protein 1 (UCP-1) positive regulators, and the UCP-1 overexpression may enhance insulin resistance and glucose transport of skeletal muscle [41]. For diabetic patients that have altered retinoid biology, vitamin A could not be effective intervention; it has been reported that insulin treatment may reverse retinoid metabolic availability. Also, intakes of vitamin A in large doses interfere with bone metabolisms and have been associated with osteoporosis [40]. Berry and Noy [42] showed that all-trans-RA has suppressive effects on insulin resistance and obesity through inducing retinoid acid receptor (RAR) gene expression and PPARβ/δ gene expression. In 2018, a study carried out by [43] reported that rats with vitamin A deficiency that were fed with diets had decreased monounsaturated fatty acid and stearoyl-CoA desaturase 1 (SCD1) levels, which alter function and structure of pancreas and increase ER stress-induced apoptosis.

4.1.2 Vitamin E for T1DM and T2DM treatment

Vitamin E is a significant constituent of antioxidant systems in every body tissue. α-tocopherol is most active type of vitamin E. Vitamin E is a group of about 8 fat soluble vitamins which four tocotrienols and four tocopherols. Vitamin E, because of its antioxidant activity, is believed to be promising therapeutic alternative T1DM and T2DM. Supplementation with vitamin E has been reported to ameliorate mouse hyperglycemia through improving secretion of insulin from alloxan-treated islet [44]. In vivo, rats with streptozotocin-induced DM were shown to present significant decrease in glucose level and improved antioxidant enzymes activities, including glutathione reductase, glutathione peroxidase, and catalase, after vitamin E supplementation. However, results obtained from human studies have been inconsistent. Vitamin E only showed effectiveness in patients that have insufficient glycemic control baseline or low-serum concentrations of vitamin E [45]. Vitamin E plays significant role in the treatment of T1DM and T2DM.

4.1.3 Vitamin D for T1DM and T2DM treatment

The most important forms of Vitamin Ds in humans are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Vitamin D is a group of fat soluble secosteroids responsible for various biological functions, including intestinal absorption of calcium, phosphate, magnesium, and other biological functions. Vitamin D3 is obtained from diets and also synthetically made in skin from 7-dehydrocholesterol when exposed to radiation of solar UVB. It is converted in the

kidney to the active vitamin D, 1,25-(OH)2 VD3 [46]. Vitamin Ds are mediated by vitamin D receptor (VDR), their nuclear receptor. Vitamin D plays significant roles in modulating T1DM and T2DM risks through having influence on inflammation, insulin sensitivity, and β-cell function [47]. Vitamin D can promote the survival of β-cell through modulating the activity and generation of cytokines via downregulation of Fas or NF-κB-related pathways. Currently, one study reported that vitamin D has increasing effects on insulin secretion stimulated by glucose through improving influx of calcium through upregulating the expression of "R-type voltage-gated calcium channel" (VGCC) genes in human and mouse islets. Treating STZ-induced diabetic rat using diet with vitamin D supplementation increased levels of insulin, decreased fasting blood glucose levels, as well as restored pancreatic islets injured by streptozotocin [48]. Meerza et al. [49] showed that treating 1,25-(OH)2 VD3 has significant changing effects on the concentrations of blood glucose and calcium, and glucose metabolic enzymes activities, such as fructose 1,6-bisphosphatase (FBPase), hexokinase, and glucose-6-phosphatase (G6Pase) in mice with induced DM. Vitamin D can have effect on insulin sensitivity in peripheral insulin-target cell through stimulating insulin receptor expression via VDR interaction or by other channels [50]. Calcium plays crucial role for any insulin-mediated intracellular process, and the extracellular and intracellular concentrations of calcium are, to a large extent, regulated by vitamin D to influence sensitivity of insulin [51].

4.2 Lycopene

Lycopene, a natural occurring carotenoid, is commonly found in tomatoes, pink grapefruit, etc.; it gives the red color. Several in vivo examinations indicated the health benefits of lycopene on T1DM and T2DM, and its accompanying complications [52, 53]. The antioxidant and anti-inflammatory properties of lycopene may be connected with its antidiabetic functions. Ali and Agha [54] carried out study with diabetic rats where lycopene supplementation resulted in a dose-dependent reduction of hydrogen peroxide (H_2O_2), lipid peroxidation, and NO, and also increased antioxidant enzymes activities, which led to decreased levels of glucose, increased levels of insulin, and enhanced profiles of serum lipids. Lycopene antioxidant properties have also indicated to solve diabetic endothelial dysfunctions in rats with induced diabetes [52]. Lycopene was evaluated for its capability to reduce cognitive decline associated with T2DM. Kuhad [55] showed dose-dependent responses to chronic treatments using lycopene, which eased cognitive impairments, decreased TNF-α and NO, alleviated cholinergic dysfunctions, and increased activity of acetylcholinesterase in rats on streptozotocin-induced diabetes. Endothelial progenitor cells (EPCs) dysfunctions are implicated in vascular complications associated with diabetes [56]. Zeng et al. [57] reported that lycopene improved AGE-induced oxidative autophagy and endothelial progenitor cells apoptosis, thereby damaging EPCs functions and number. Based on the knowledge about lycopene and T2DM, it is clear that lycopene could have promising potentials for improving T2DM vascular complications. Li et al. [53] carried out a study on rats with streptozotocin- (STZ) induced diabetes for studying lycopene specific therapeutic effects on diabetic nephropathy. They reported that lycopene has protective effects on kidney against DM-induced morphological destructions as well as impairments of functions through regulating growth factor of connective tissue, increasing protein kinase B (Akt) phosphorylation, and improving oxidative status. A different study showed that lycopene ameliorates renal functions through interruption of the Advanced glycation end products (AGE)-receptor for advanced glycation end-products (RAGE) (AGE-RAGE) axis [58].

Table 2 shows bioactive compounds, dietary nutrients, and their sources for T1DM and T2DM treatment.

Plants and sources of the compounds	Bioactive Compound	Phytochemical class	T1DM and T2DM properties	References
Asparagus, buckwheat, figs, apples, etc.	Rutin	Polyphenol (flavonoid)	Rutin reduced levels of blood glucose in insulin-resistant mouse by improving GLUT4 translocation and activities of insulin-dependent receptor kinase	[59]
Vitamin D3 (Cholecalciferol) is obtained from diets (fatty fishes, cooked egg yolk, liver, fungi) or synthetically made in skin when exposed to solar UVB.	Vitamin D	Vitamin	Treating streptozotocin-induced diabetic rat using diet with vitamin D supplements decreased fasting blood glucose levels, increased levels of insulin, as well as restored pancreatic islets injured by STZ	[48]
Citrus fruits, such as lemons, oranges, etc., and few plants	Hesperidin	Polyphenol (flavonoid glycoside)	It has protective effects in diabetic nephropathy, often through inhibiting transforming growth factor-β1- (TGF-β1-) integrin-linked kinase- (ILK-) Akt signalling	[60, 61]
Cod liver oil, carrots, broccoli leaf, liver (fish, pork, beef), sweet potato, spinach, etc.	Vitamin A, including provitamin A compounds	Vitamin	Increases levels of insulin mRNA and secretion of insulin in cultured islets, through raising pancreatic glucokinase by activating glucokinase promoter. Retinol and retinoic acid are uncoupling protein 1 (UCP-1) positive regulators; UCP-1 overexpression could enhance insulin resistance and glucose transport	[41]
Fruits, flowers, vegetables, etc.	Anthocyanin	Polyphenol (flavonoid)	In STZ-induced diabetic rats, pelargonidin (an anthocyanin) injection improved glucose tolerance, normalized elevated levels of blood glucose, and improved serum insulin level	[62]
Grapefruit, pumelo, tomatoes, grapefruit juices, etc.	Naringin	Polyphenol (flavonoid)	Naringin protects cells against high glucose-induced destruction. Naringin inhibits high inflammatory reaction induced by glucose through mediating oligomerization and nucleotide-binding domain-related receptors family of inflammasome of pyrin domain-containing 3 in mesangial cells of rat	[63]
Grapefruit, oranges, lemon, tomatoes, etc.	Naringenin	Polyphenol (flavonoid)	Naringenin ameliorated structural changes and renal damages, including glomerulosclerosis in STZ-	[64]

Plants and sources of the compounds	Bioactive Compound	Phytochemical class	T1DM and T2DM properties	References
			induced diabetic rats, possibly via downregulating IL-1 and TGF-β1 through decreasing oxidative stress, modulating production of proinflammatory cytokines and apoptotic events	
Green tea, black tea, white tea, onions, apple skin, plums, etc.	Epigallocatechin gallate	Polyphenol (Catechin)	Epigallocatechin gallate supplementations have influence on expression of the genes involved in metabolism of lipid and glucose in liver, such as through increasing glucose kinase by mRNA expression and reducing mRNA expressions of G6Pase, fatty acid synthases, as well as PEPCK	[65]
Turmeric plant (*Curcuma longa*)	Curcumin	Polyphenol	Curcumin oral administration reduced blood glucose levels, increased levels of plasma insulin, and reduced body weight	[66]
Red onions, apples, tea, broccoli, etc.	Quercetin	Polyphenol (flavonoid)	Quercetin increased glucose uptakes in cultured skeletal muscle cell by stimulating GLUT4 translocation through 5' AMP-activated protein kinase activation. Quercetin has activities on homeostasis of glucose in skeletal muscle and liver.	[67]
Red wines, grape skins, seeds, groundnut skins, etc.	Resveratrol	Polyphenol	In insulin-secreting cell, treatment with resveratrol improved mitochondrial activity, improved insulin secretion stimulated by glucose, and enhanced glucose metabolism.	[68]
Soybeans, fava beans, chickpeas, etc.	Genistein	Polyphenol (isoflavone)	Supplementation with genistein alleviated hyperglycemia induced by streptozotocin and improved insulin levels and glucose tolerance	[69]
Tomatoes, pink grapefruit, etc.	Lycopene	Carotenoid	Lycopene antioxidant activities have demonstrated to solve diabetic endothelial dysfunctions in diabetic rats	[52]
Wheat germ oil, sunflower oil, rapeseed/canola oil, almonds, g hazelnut oil, etc.	Vitamin E	Vitamin	After vitamin E supplementation, rats with streptozotocin-induced DM, in vivo, were shown to present significant reduction in glucose level and improved	[44]

Plants and sources of the compounds	Bioactive Compound	Phytochemical class	T1DM and T2DM properties	References
			antioxidant enzyme activities, such as catalase, glutathione peroxidase, and glutathione reductase.	

Table 2.
Medicinal plants, bioactive compounds, nutrients with effectiveness against T1DM and T2DM.

4.3 Polyphenolic compounds and their properties against T1DM and T2DM

Several polyphenols have been directly linked to treatment of T1DM and T2DM, including resveratrol, epigallocatechin-3-gallate (EGCG), quercetin, genistein, hesperidin, naringin, anthocyanins, curcumin, rutin, naringenin, etc.

4.3.1 Resveratrol properties against T1DM and T2DM

This polyphenol occurs naturally in red wines, seeds, grape skins, and groundnut (peanut) skins. In insulin-secreting cell, treatment with resveratrol improved insulin secretion stimulated by glucose, improved mitochondrial activity, and enhanced glucose metabolism [68]. The effects depend on active Sirtuin 1-induced key genes upregulation for β-cell functions [68]. Resveratrol exhibits anti-inflammatory and antioxidant properties, and also maintains metal homeostasis and increases mitochondrial function [70]. Resveratrol lower production of hepatic glucose, improve insulin sensitivity, and normalize hyperglycemia through Sirtuin 1 activation [71]. A study done recently suggest that T2DM was improved by resveratrol through the regulation of lipid metabolism, mitochondrial biogenesis, and β cells via SIRT1 activation [72]. Animal and cell studies suggest that resveratrol could have potentials in T1DM and T2DM treatment [73]. A NAD + -dependent deacetylase known as Sirtuin 1 (SIRT1) is known to be involved in regulating several factors which affect T2DM; resveratrol has been shown to be SIRT1 activator [71].

4.3.2 Epigallocatechin-3-Gallate (EGCG) properties against T1DM and T2DM

Epigallocatechin-3-gallate, a polyphenol, is obtained from numerous plants, especially green teas, black tea, white tea, and apple skin. Studies have been done on green tea health benefits, with the benefits associated with epigallocatechin-3-gallate, which is most abundant constituent. EGCG has strong antioxidant activities. Han [74] reported that epigallocatechin-3-gallate protected cells of RINn5F against β-cell damage caused by cytokines. The molecular mechanisms may include suppressing expression of iNOS via the inhibition of the activation of NF-κB. Consequently, epigallocatechin-3-gallate can improve pancreatic functions. Cytokines made by immune cell might cause damage of β-cell in insulin-dependent DM, and have been attributed to NO and iNOS generation in the cells. EGCG antioxidant effects are contentious; some evidence suggested that EGCG is prooxidant [75]. A typical example is the report of the work done by [75] showed that EGCG mediated the H_2O_2 production and triggered the formation of Fe2 + −dependent toxic radicals, which caused cell apoptosis and reduced the viability of cell in pancreatic β cells of HIT-T15.

4.3.3 Quercetin properties against T1DM and T2DM

Quercetin is a flavonoid which occurs naturally in many foods such as red onions, tea, apples, etc. A study indicated that treatment with quercetin enhanced lipid and

glucose metabolism, as well as eased hepatic histomorphological damage in rats with STZ-induced DM, which possibly connected to the SIRT1 activity upregulation by quercetin and its impacts on Akt signaling pathways [76]. Vascular complications have been associated with most mortality and morbidity in T1DM and T2DM patients [77]. Youl et al. [78] carried out research and reported that quercetin improved secretion of glucose-induced insulin and protected β-cell viability/function from hydrogen peroxide-induced oxidative damages in cells of INS-1. The effects are mediated by extracellular signal regulated kinase (ERK1/2) phosphorylation, which suggest that activation of extracellular signal regulated kinase take part in quercetin action [78]. Quercetin has antiapoptotic, anti-inflammatory, and antioxidant effects, and has been shown to have potentials for diabetes treatment, as well as its health complications [67, 76, 77]. Quercetin also has influence on homeostasis of glucose in skeletal muscle and liver; quercetin increased glucose uptakes in cultured skeletal muscle cell by stimulating GLUT4 translocation through 5' AMP-activated protein kinase (AMPK) activation [67]. In the same way, quercetin in hepatocytes activated 5' AMP-activated protein kinase, and was associated with glucose-6-phosphatase suppression, finally reducing the production of hepatic glucose [67].

4.3.4 Genistein properties against T1DM and T2DM

Genistein, a naturally occurring compound, structurally belongs to a group of compounds known as isoflavone. Genistein is found in many plants such as soybeans, chickpeas, etc. [79]. Evidence support genistein as a therapeutic potential and preventive treatment for T1DM and T2DM [69, 80, 81]. Genistein dietary supplementation enhanced mass of β-cell through reducing apoptosis and increasing the proliferation of β-cell [69]. The genistein supplementation alleviated hyperglycemia induced by streptozotocin (STZ) and improved insulin levels and glucose tolerance [69]. Recently, [82] showed that genistein decreased fasting glucose levels, prevented cytosolic phosphoenolpyruvate carboxy kinase (PEPCK), and activated ERK1/2 and AMPK pathways in mice with alloxan-induced diabetes, which could, as a result, improve dysfunctions in T1DM and T2DM associated hepatic gluconeogenesis. Mass loss in functional β-cell, which reduces secretion of insulin, is important for T2DM development. The β cells mass is regulated by balance between apoptosis, proliferation, transdifferentiation, and neogenesis [80]. Ae Park et al. [81] studied genistein antidiabetic effects on C57BL/KsJ-db/db mice that share human-like T2DM metabolic features. HbA1c and blood glucose were reported to be significantly lower in groups of genistein, whilst glucagon-insulin ratio and glucose tolerance were also enhanced in the group of genistein in comparison with control group [81]. Also, the supplements of genistein improved the total cholesterol, free fatty acid, HDL-cholesterol, and plasma triglyceride levels in the mice. The effects could be due to increased activities of hepatic glucokinase, and also due to the decreased activities of G6Pase, β-oxidation, and hepatic fatty acid synthase [81]. Consequently, genistein could have antidiabetic effects against T1DM and T2DM through improving the metabolism of glucose and lipid. Fu et al. [69] showed that incubation of genistein induced increase in the proliferation of human islet β-cell and INS-1 through activating cAMP/PKA-dependent extracellular signal regulated kinase (ERK1/2) signaling pathway. Studies involving animal models showed that genistein has antidiabetic effects; particularly, [69] showed that STZ-induced diabetes reduced mass of β-cell and caused cell architecture disruption.

4.3.5 Hesperidin properties against T1DM and T2DM

Hesperidin, a flavonoid glycoside, is commonly found in citrus fruits, e.g. lemons and oranges, in rich quantity. Hesperidin oral administration significantly

decreased HbA1c and glucose levels and raised serum insulin, vitamin E, and vitamin C levels in rats with HFD/STZ-induced diabetes [83]. The effects were most likely as a result of decline in producing oxidants and proinflammatory cytokines, including IL-6 and TNF-α [83]. In vivo and in vitro studies showed that hesperidin helps in T2DM treatment and prevention, and complications associated with T1DM and T2DM, via its antidepressant, anti-inflammatory, and antioxidant properties [61, 83, 84]. In pancreatic islet cells of rat, hesperidin has been reported to protect against IL-1β-induced oxidative stress, thus improving islet cells function and restoring insulin secretion and biosynthesis [84]. Hesperidin treatment in rats with STZ-induced diabetes attenuated plasma and retina abnormalities, such as increased breakdown of blood retina and decreased retina thickness, through its anti-inflammatory and antioxidant properties, and the inhibition of AGEs production and high aldose reductase [85]. Hesperidin treatment in rats on high fat diet (HFD)/STZ-induced diabetes decreased hyperglycemia through increasing the uptake of peripheral glucose, which may be attributed to GLUT4 mRNA expression upregulation [84].

4.3.6 Naringin properties against T1DM and T2DM

Naringin, also a flavonoid, is commonly seen in some grapefruits and citrus species. It is known for its antihyperglycemic, antioxidant, and anti-inflammatory properties [86]. Numerous studies recently conducted demonstrated that naringin may improve T1DM and T2DM and ameliorate the severity of their associated health complications; their mechanism is understood [63, 86]. In vitro studies showed that naringin protects cells against high glucose-induced destruction. A typical example is the work done by [63], which showed that naringin inhibits high inflammatory reaction induced by glucose through mediating the oligomerization and nucleotide-binding domain-related receptors family of inflammasome of pyrin domain-containing 3 (NLRP3) in mesangial cells of rat. Sharma et al. [87] showed that naringin ameliorated kidney damage and hepatic steatosis, and attenuated β-cell dysfunction and insulin resistance through reducing inflammation and oxidative stress by upregulating PPARγ, heat shock protein-72, as well as heat shock protein-27. Li et al. [88] showed that naringin can protect the endothelial cells of humans against high damage induced by glucose through improving mitochondrial function, downregulating chemokine (C-X3-C motif) ligand 1 (CX3CL1), and inhibiting oxidation. In addition, many studies have showed naringin beneficial effects on complications of diabetes such as diabetes-associated anemia, atherosclerosis, cognitive decline, and kidney damage [89, 90]. Mahmoud [89] showed that naringin protected rats with HFD/STZ diabetes from diabetes-induced anemia through stimulation of adiponectin expression and reducing the production of proinflammatory cytokine. In rats with NA/STZ-induced DM, naringin significantly ameliorated the serum glucose levels and profile of the lipid, including low density lipoprotein cholesterol (LDL), and free fatty acids (FFAs) [86]. The effects could be potentiated through elevation in glycogen phosphorylase and liver G6Pase activities, enhancing response to insulin secretion, and improving GLUT4 expression, adiponectin, and insulin receptor, in addition to reducing oxidative stress [86].

4.3.7 Anthocyanins properties against T1DM and T2DM

Anthocyanins (ANTs) are flavonoids mostly responsible for purple, blue, and red colors of fruits, flowers, and vegetables [91]. Most anthocyanins have strong antioxidant properties which may play role in their antidiabetic activities against

T1DM and T2DM. In rats with STZ-induced diabetes, pelargonidin (an anthocyanin) injection improved serum insulin level, improved glucose tolerance, and normalized elevated levels of blood glucose [62]. Yan et al. [92] reported that anthocyanins pre-treatment attenuated β-cell autophagy mediated by H_2O_2 through antioxidant transcription factor Nrf2 activation. In cells of HepG2, mulberry anthocyanins extracts were reportedly found to alleviate insulin resistance through PI3K/Akt pathways activation [93]. Zhang et al. [94] indicated that anthocyanins from extracts of Chinese bayberry upregulated expression of HO-1 through activating ERK1/2 and PI3K/Akt signaling in cells of INS-1. Consequently, anthocyanins protected the cells against β-cell injury induced by H_2O_2.

4.3.8 Curcumin properties against T1DM and T2DM

Curcumin, a polyphenol, is extracted from dried root of turmeric plant (*Curcuma longa*). Curcumin has numerous pharmacological activities in which anti-inflammatory and antioxidant properties are most notable properties [95]. The main factors in T1DM- and T2DM-related hepatic fibrogenesis are hepatic stellate cells (HSCs) [96]; in HSCs, AGEs induce gene expression of RAGE that may stimulate HSCs activation [96]. Lin et al. [95] showed that curcumin inhibited AGE stimulation possibly through increasing PPARγ gene expression which ameliorated RAGE expression, and eased oxidative stress. A study showed that curcumin oral treatment increased levels of plasma insulin, reduced blood glucose levels, and reduced body weight [63]. Study indicated that curcumin ameliorated glucose/lipid metabolic disorder and enhanced insulin resistance in diabetic rats; the effects may be attributed to the decrease in the TNF-α and free fatty acid in serum [97]. Curcumin has significant effects against T1DM and T2DM. Through scavenging free radicals, curcumin protects pancreatic islet against oxidative stress induced by streptozotocin. Curcumin increased insulin secretion, increased islet viability, reduced concentration of ROS, reduced NO generation, and inhibited poly ADP-ribose polymerase-1 overactivation. Oral curcumin in db/db mice alleviated hyperglycemia-induced kidney/liver damage via mitochondrial function normalization, by suppressing lipid peroxidation and NO synthesis [98].

4.3.9 Rutin properties against T1DM and T2DM

Rutin is a flavonoid commonly found in several fruits and vegetables, including asparagus, buckwheat, figs, and apples. Rutin is known to have many biological properties such as antioxidant, neuroprotective, antihyperglycemic, and anti-inflammatory properties [99], and all support its potential applications in the prevention and treatment of T1DM and T2DM and their associated health complications. Rutin reduced glycogen phosphorylase and G6Pase activities and increased hepatic hexokinase activities [47]. To this effect, rutin might decrease output of hepatic glucose. In rats with nicotinamide-STZ-induced diabetes, rutin administration decreased serum glucose levels, ameliorated glucose tolerance significantly, ameliorated oxidative stress, and also improved serum lipid variables, including serum total lipids, triglycerides, VLDL-cholesterol, and LDL-cholesterol. Rutin antihyperglycemic effects could be accomplished through increasing the uptake of glucose by peripheral tissue, stimulating secretion of insulin, suppressing gluconeogenesis in liver, and improving insulin resistance. Hsu et al. [59] showed that rutin decreased levels of blood glucose in insulin-resistant mouse by improving GLUT4 translocation and activities of IRK (insulin-dependent receptor kinase).

4.3.10 Naringenin properties against T1DM and T2DM

Naringenin, another flavonoid, naturally occur in citrus fruits, including oranges, tomatoes, grapefruits, and lemons [100]. Due to its beneficial effects in treating T1DM and T2DM and their associated health complications, naringenin has recently gained more attention. Several studies have evaluated naringenin role in complications associated with T1DM and T2DM, including vascular disease, neuropathy, hepatotoxicity, cardiac hypertrophy, and nephropathy [101, 102]. Kapoor and Kakkar [101] showed that increased apoptotic proteins expression, mitochondria dysfunction, increased ROS generation, altered antioxidant status, and altered activities of kidney and liver enzymes; may induce diabetic hepatopathy and liver damage in rats with T2DM; all the effects were completely rescued after treatment with naringenin. Consequently, naringenin has promising potentials for diabetic hepatopathy treatment. Naringenin functioned as cholinesterase inhibitor and as antioxidant, ameliorating diabetes-induced dysfunctions in memory of rats [103]. Roy et al. [64] reported that naringenin ameliorated renal damage and structural changes, including glomerulosclerosis in rats with STZ-induced diabetes, likely via downregulating IL-1 and TGF-β1 through decreasing oxidative stress, modulating the production of proinflammatory cytokines and apoptotic events. They reported that naringenin ameliorated endothelial dysfunctions induced by glucose through reducing apoptosis and oxidative stress through NO and ROS/caspase-3 pathways in endothelial cell [64, 102]. In rats with STZ-induced diabetes, naringenin oral administration improved VLDL concentrations, normalized LDL, and reduced blood glucose levels, as well normalized oxidative stress in pancreas and liver; the effects have been associated with increased mRNA expression and increased protein levels of PPARγ and GLUT4 by naringenin [104].

5. Epigenetic modification actions of bioactive compounds and dietary nutrients in T1DM and T2DM

Epigenetic modification is heritable and persistent changes in DNA which regulate how the expression of genes are done, with no effects on the sequence of the nucleotide itself. Epigenetic modification includes DNA methylation, microRNA regulation, and histone modification. It has been generally acknowledged that epigenetic and genetic factors predispose to T1DM and T2DM. The main genes which regulate the differentiation of β-cell, including GLP1 receptor, PDX1, and PAX4, are epigenetically regulated. To prevent or alleviate symptoms of hyperglycemia, preventive strategies using nonpharmacological measures have been employed. Weight loss, regular exercise, and healthy diet can help manage glucose serum level and also enhance normal metabolism of glucose. Pancreatic islets can be transplanted [105]. Epigenetic modification encourages insulin resistance via having pro-inflammatory effects on numerous biological factors, such as osteopontin, NF-kB, and Toll-like receptors [106, 107]. Some of the bioactive compounds and dietary nutrients associated with the epigenetic modification in T1DM and T2DM are shown in **Table 3**.

Bioactive compounds, including EGCG, resveratrol, curcumin, sulforaphane, lycopene, etc., have been reported to modify epigenetic mechanisms, which could result in increased cells sensitivity to conventional agents [118]. Quercetin is a bioactive compound in buckwheat and citrus fruits. The bioactive compound functions as DNMT1 inhibitor through repressing TNF-induced NFkappa transcription factor and also encourages Fas ligand associated apoptosis through histone H3 acetylation, in addition to potential inhibition of HDAC [119]. Quercetin has been reported to take part in glucose uptake stimulation via MAPK insulin-dependent

Plants and natural sources of the compounds	Bioactive compound	Phytochemical group	Epigenetic modification effect	Reference
Apples, black tea, grapes, blackberries, etc.	Epigallocatechin gallate	Polyphenol (flavonoids)	Chromatin remodelling, histone acetylation, DNA methylation	[108, 109]
Broccoli, cabbages, Brussels sprouts, etc.	Sulforaphane	Isothiocyanate	DNA methylation	[110]
Cod liver oil, liver, carrots, broccoli leaf, sweet potato, spinach, etc.	Vitamin A	Vitamin	Changes chromatin structure	[111]
Fatty fishes, liver, fungi, cooked egg yolk. Synthetically made in skin when exposed to solar UVB	Vitamin D	Vitamin	Changes chromatin structure	[112]
Grapes, chocolate, grape skins, red wines, seeds, peanut skins, etc.	Resveratrol	Polyphenol	miRNA levels modifications, chromatin remodelling, histone modifications	[113]
Turmeric plant (*Curcuma longa*)	Curcumin	Polyphenol	miRNA levels modifications, chromatin remodelling, histone modifications	[114]
Red onions, broccoli, apples, tea, etc	Quercetin	Polyphenol (flavonoid)	Histone modifications	[67]
Rice, fat fraction of bran, rice bran oil, etc.	ϒ-oryzanol	Lipid	DNA methylation	[115]
Soybeans, chickpeas, beans, fava, etc.	Genistein	Polyphenol (isoflavone)	Histone modifications, DNA methylation	[116]
Soybeans, chickpeas, fava, etc.	Genistein	Polyphenol (isoflavone)	DNA methylation	[116]
Tomatoes, pink grapefruit, etc.	Lycopene	Carotenoid	DNA methylation	[117]

Table 3.
Medicinal plants, nutrients, and bioactive compounds in epigenetic modification in T1DM and T2DM.

mechanisms. This is achieved in muscles through translocating GLUT4 transporters and in the liver through downregulating key enzymes of gluconeogenesis [67]. Resveratrol is a polyphenol which naturally occurs in grapes, chocolate, etc. Resveratrol activates a NAD-dependent HDAC, called sirtuin 1 (SIRT1); administration of SIRT1 to animals with insulin resistance regulates insulin sensitivity and improves glucose homeostasis [113]. Curcumin inhibits DNMTs, HDACs, and HATs. It inhibits or activates many miRNAs [120]. Epigallocatechin gallate (EGCG), an abundant catechin in green tea, is known to affect T1DM and T2DM. Epigenetic action mechanism of EGCG involves DNA methylation, histone acetylation, and deacetylation. Epigallocatechin gallate upregulates activities of anti-inflammation of regulatory T cell [108]. Genistein, a polyphenol obtained from soybean, induces active histone modifications and reverses hypermethylation [121]. Genistein appears to modulate on T1DM and T2DM through having direct effects on protection against apoptosis, glucose-stimulated insulin secretion, and β-cell proliferation. These have been reported to modulate through epigenetic

mechanisms and to involve cascades of cAMP/PKA signaling [116]. Sulforaphane obtained from broccoli is a bioactive compound with epigenetic effects. Sulforaphane was reported to inhibit HDACs, decrease promoter methylation, and inhibit expression of DNMT1 in T2DM [122]. *in vivo* studies of cell culture, co-expression network analysis, and analysis of genetic data of liver tissues indicated that sulforaphane inhibits production of glucose via nuclear translocation mechanisms of "nuclear factor erythroid 2-related factor 2" (NRF2) as well as inhibiting gene expression of essentials enzymes involved in gluconeogenesis [110]. Lycopene in tomatoes and organosulfur compounds in allium and garlic have anti-diabetic effects, especially against T2DM. These bioactive substances were reported to modulate through inducting histone acetylation in numerous malignancies. Lycopene is a carotenoid in tomatoes which has potent antioxidant properties. Studies reported a usefulness in using lycopene to ameliorate oxidative stress in patients with T1DM and T2DM [117]. Lycopene was reported to act through gene methylation. Bioactive compounds have epigenetic modification role in T1DM and T2DM.

6. Conclusion and future perspective

Diabetes mellitus (DM), simply called diabetes, are metabolic disorders characterized by varying or persistent hyperglycemia (high levels of sugar in the blood) over an extended time period. About 463 million people have diabetes worldwide; estimates project 700 million people by 2045. Over 90 to 95% of DM cases are T2DM, while the remain 5 to 10% are other types of DM, including T1DM, the gestational diabetes, and other minor specific types rarely encountered. Medicinal plants, bioactive compounds, and dietary measures have been found to be effective in the treatment of T1DM and T2DM. While T1DM is caused by the loss of beta cells of pancreatic islets that produce insulin, resulting in the deficiency of insulin, T2DM is caused by insulin resistance, and could combine relative reduction in the secretion of insulin. *Aloe vera, Terminalia chebula, Perilla frutescens, Curcuma longa, Zingiber zerumbet, Nigella sativa, Gongronema latifolium, Pachira aquatic, Caesalpinioideae, Azadirachta indica, Abelmoschus moschatus, Cinnamomum verum, Salvia officinalis, Tinospora cordifoli, Pterocarpus, Ocimum tenuiflorum, Mangifera indica, Syzygium cumini, Coccinia grandis, Caesalpinia bonduc, Gymnema sylvestre, Carthamus tinctorius, Allium sativum,* and *Trigonella foenum-graecum* are among the medicinal plants shown to be effective in controlling and treating T1DM and T2DM. Bioactive compounds such as lycopene, vitamin E, vitamin D, genistein, quercetin, resveratrol, epigallocatechin-3-gallate, hesperidin, naringin, anthocyanin, etc. are useful in treating T1DM and T2DM. There is need to explore other treatment measures, both medicine and alternative medicine, for T1DM and T2DM treatment. Medicinal plants and their bioactive constituents provide excellent potentials for the development of drugs and therapeutic measures for treating diabetes mellitus in general.

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Conflict of interest

The author declares no conflict of interest.

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