Popular functional foods and herbs for the management of type-2-diabetes mellitus: A comprehensive review with special reference to clinical trials and its proposed mechanism

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ABSTRACT

Diabetes mellitus (DM) and its related complications are the serious public health concern globally. This is the first review highlight on major functional foods and herbs with anti-diabetic activity particularly focus on type 2 diabetes mellitus (T2DM) with special reference to clinical trials and their proposed anti-diabetic mechanisms. This contribution summarizes the current prevalence of DM, etiology and pathophysiology, complications related to DM, current conventional treatment regimen for T2DM as well as complimentary therapy for anti-DM activity (functional foods/herbs-nutraceuticals). Based on the literature survey, authors conclude that coinagen of functional food/herbs (adjuvant therapy) with a conventional hypoglycemic drug with modiﬁed lifestyle pattern could signiﬁcantly improve glycemic control and abolish DM associated complications. Nevertheless, further clinical trials are required to conﬁrm the safety and efﬁcacy of different functional food/herbs with the conventional hypoglycemic drug (holistic) especially the dosage/duration/mode of administration are crucial to avoid adverse effect and to improve glycemic control.

1. Introduction

Diabetes mellitus (DM) is a group of chronic metabolic disorders or diseases characterized by a persistent increase in blood glucose level (hyperglycemia). If not treated well it might affect various organs (heart, vascular, renal, neuron, eye) and leads to various life-threatening complications or even death (Mirmiran, Bahadoran, & Azizi, 2014). The incidence of DM is considerably increasing all over the world, and International Diabetic Federation (IDF) estimated that roughly 592 million people might be affected by DM by the year 2035 (Guariguata et al., 2014). Increased urbanization, aging, modiﬁed lifestyle pattern (lack of exercise and awareness, smoking) results in obesity and thus increase the prevalence of cardiovascular diseases (CVDs) and DM in developing and developed countries (Deshpande, Harris-Hayes, & Schootman, 2008). Moreover, the prevalence of DM in Asia (almost 60%) mainly in Taiwan, Hongkong, and China are exponentially increased in recent years (Wu, Meng, Wild, Gasevic, & Jackson, 2017). The cost of health care for DM patients are increasing enormously due to hospitalization/consultation as well as various treatment procedure (surgery/medi-surgery, drugs, and insulin) which impose an economic burden for the DM patients and their counties as well (World Health Organization (2016) (2016), 2016).

Two major types of DM include Type 1 DM (insulin dependent) and Type 2 DM (Insulin independent). Type 1 DM is characterized by an absolute deﬁciency in the production of insulin due to the complete destruction of β cells of pancreas it may be due to epigenetic (autoimmunity/mutation) or acquired. T1DM represents only 10% of all diabetes case it affects all age, but the majority are kids less than 5 years old (Atkinson, Eisenbarth, & Michels, 2014; Ozougwu, Obimba, Belonwu, & Unakalamba, 2013). T2DM is a common DM, which accounts for 90% of DM, it is also characterized by prolonged increase in blood glucose level (chronic hyperglycemia) due to defect in either insulin secretion (impaired β cell function) or its receptor (insulin resistance) (Li et al., 2019). Other minor types of DM are gestational diabetes mellitus (GDM) occur during pregnancy due to high blood glucose concentration. The common signs and symptoms of diabetes are polyuria (increased urination), polydipsia (increased thirst) and weight loss (due to excessive oxidation/glycation of proteins). Other minor types of DM are Gestation DM (Kohei, 2010). This contribution was aimed to highlight the anti-diabetic activity of popular functional foods and herbs (medicinal plants) with special reference to clinical trials and their proposed anti-diabetic
mechanisms. Also, this review summarizes the etiology and pathophysiology, complications related to DM, current conventional treatment regimen for T2DM as well as complimentary therapy for anti-DM activity.

1.1. Etiology and pathophysiology of DM

Studies has suggested that genetical and environmental factors (epigenetic) are the main factors that contribute to DM (Hu, 2011). Since DM is a group of chronic multifactorial metabolic disorder or diseases with unclear pathophysiology. However, few known factors that might contribute to DM are discussed below. T1DM has a strong correlation with endocrine autoimmune (auto-antibodies especially ICA), which is caused due to genetical factor. (Atkinson et al., 2014). Whereas, T2DM is a heterogeneous disorder caused by the combination of genetical and environmental factors. The major environmental factors that contribute to T2DM are obesity (increased visceral fat), aging, decreased muscle mass, excessive consumption of simple sugars, imbalance in hormone owing to altered sleeping pattern and psychological stress as well as smoking/excess alcohol intake (Gauriguda et al., 2014; Kohei, 2010). Blood glucose homeostasis was regulated by several factors especially the hormones like insulin and glucagon. During T2DM the glucose homeostasis is lost due to dysfunction of β cells or impaired insulin function (receptor/substrate modulation mutation) which results in increased hepatic glucose production (endogenous glucose), oxidative stress (production of advanced glycation endproducts; AGEs), inflammation (endothelial dysfunction) and followed by impaired glucose tolerance (IGT) and results in insulin resistance (less glucose utilization). During IGT various insulin signaling pathway genes/proteins (AMP related protein kinase; AMPK, peroxisome proliferator activated receptor; PPAR, serine protein kinase B/Phosphatidylinositol-3-Kinase; Akt/PI3K) are affected and thereby decrease the glucose utilization capacity (peripheral tissue) and finally results in hyperglycemia, hyperlipidemia, and T2DM (Kohei, 2010; Ozougwu et al., 2013). Impaired insulin activity (insulin deficiency) in T2DM results in various metabolic derangements such as modified carbohydrate metabolism (decreased glucose uptake by peripheral tissues, increased glycogenesis and gluconeogenesis), lipid metabolism (increased lipolysis and decreased lipogenesis) and protein metabolism (increased protein synthesis and muscle loss) (Kohei, 2010; Vella & Rizza, 2003).

1.2. Complications of DM

Chronic hyperglycemia can result in various long-term and life-threatening complications including microvascular and macrovascular complications. As mentioned earlier that chronic hyperglycemia may trigger cascade of pathological events like oxidative stress, formation of AGEs (Oxidation of proteins/glycation of protein), hypertension, inflammatory response, neovascularization, vascular/endothelial dysfunction (increased vascular permeability by AGEs and activation of protein kinase C; PKC), dyslipidemia and thus affects various organs like nerves, heart, eye, kidney and endothelium (Chawla, Chawla, & Jaggi, 2016; Rahimi-Madiseh, Heidarian, Kheiri, & Rafieian-Kopaei, 2017). Macrovascular complications include cardiovascular and cerebrovascular events like coronary artery disease (CAD-myocardial infarction), stroke, cognitive impairment, and peripheral arterial disease (PAD- foot ulcer, gangrene) and microvascular complications include diabetic nephropathy (microalbunimuria/renal failure), retinopathy (cataract) and neuropathy. (Fowler, 2008).

1.3. Insulin sensitivity or resistance

The reduced sensitivity to insulin is called insulin resistance. The exact mechanism behind insulin sensitivity or resistance has not fully explored. However, many researchers have illustrated numerous mechanism for insulin sensitivity/resistance including abnormal insulin secretion, insulin antagonist, altered or mutated insulin signaling pathway (Akt/AMPK and PPAR) by altered receptor/substrate (Insulin specific receptor; INSR/Insulin receptor substrate; IRS via high mobility group A1; HMGAI transcriptional factor), activation of suppressors of cytokines signaling (SOCS-1; Compete with IRS and block insulin signaling) defect in post-receptor signaling and increased activity of phosphatases (Protein tyrosine phosphatase 1B; PTP1B and Phosphatase and tensin homolog; PTEN). Those above indicated modifications are mainly due to hyperlipidemia/obesity (accumulation of fat in adipose tissue), which results in increased release of adipocytokines, oxidative stress, and inflammatory response and subsequently results in obesity-related insulin resistance (Chang et al., 2013; Vinayagam & Xu, 2015).

2. The current treatment regimen for T2DM

Currently, different treatment regimens are used to manage DM especially the usage of hypoglycemic drugs, insulin injection (IM) as well as surgical treatments (bariatric). However, hypoglycemic drugs are highly preferred (first line medication) followed by insulin therapy and surgical procedure (Kaur, Fernandez, & Sim, 2017). Hence, American diabetes association (ADA) recommended a success formula for treating or management of T2DM is by consumption of oral antidiabetic drug with or without insulin therapy along with balanced diet (low carb) or nutritional therapy (supplementation-micro and macronutrients) and modified lifestyle (regular exercise) (American Diabetes Association, 2018a). The anti-hyperglycemic mechanism of various hypoglycemic drugs is elaborated in Table 1. These standard hypoglycemic drugs have few flaws as they have higher resistance (limited efficacy) in many DM patients and cannot regulate various other related complications like dyslipidemia, obesity, hypertension, endothelial dysfunction as well as trigger multiple adverse effects including weight gain, hypoglycaemia, peripheral edema, anaemia, renal and hepatic toxicity, abdominal discomfort (diarrhoea, vomiting, nausea, dysentery, constipation, bloating), lactic acidosis and also expensive as well. Hence the demand for alternate natural hypoglycemic drugs was of in high need for managing DM (Tanveer, Akram, Farooq, Hayat, & Shafi, 2017).

3. Alternative or complimentary therapy for managing DM

3.1. Herbs (Phytotherapy/phytomedicine) for management of T2DM

For several years the traditional medicinal practitioners (complementary medicine therapist) prescribed the plant-based drug for treating various disease conditions as it is cheap and shows less toxicity or adverse effects (Jamshidi-Kia, Lorigooini, & Amini-Khoei, 2018). Most of the plant-based drugs (alone or polyherbal formula) are supplemented as adjuvant therapy for various non-communicable diseases like DM, cancer, CVDs, and dyslipidemia (Asgari et al., 2012; Ghorbani, 2014; Khan et al., 2012). Since DM is a multifactorial disease, and hence it need many active components/drugs to treat various complications related to DM. Several studies have reported the anti-diabetic and insulin modulatory potentials in various herbs and food products (Khan et al., 2012; Tanveer et al., 2017). Fig. 1 represents the anti-diabetic activity (brief mechanism) of various functional foods/herbs/nutraceuticals in organ specific manner. Moreover, ADA and WHO has recommended to intake healthy foods (nutraceuticals/herbal extract and functional food) to the management of T2DM (American Diabetes Association, 2018b). In this review, the authors mostly concentrated on popular herbs used by traditional medicinal practitioners in Asia (especially China, Taiwan, and India).

3.1.1. Ginkgo biloba (Maidenhair tree)

Ginkgo biloba is a tree (oldest of all trees) belong to family
Ginkgoaceae. Its leaves and barks are traditionally used to improve cognitive function, immunity as well as to treat tinnitus, sexual dysfunction, migraine and common cold. Major phytocomponents of Ginkgo biloba are flavonoid glycosides, terpenes lactones, ginkgolic acid and EGb 761 (Napryeyenko, Sonnik, & Tartakovsky, 2009; Rhee et al., 2015).

Ginkgo biloba shows antioxidant, anti-inflammatory, hypolipidemic, anti-obesity, anti-tumor activities (Aziz et al., 2018; Rudge et al., 2007).

Hypoglycemic effect of Ginkgo biloba is endorsed by inhibiting the synthesis of α-glucosidase (Pinto et al., 2009), anti-AGEs (glycation-via Nrf2 pathway), increased peripheral glucose uptake via positively regulating AMPK signaling pathway (Aziz et al., 2018). Also reported to positively regulate the expression of PPAR-α/γ and thus induce lipoprotein lipase (LPL) expression and hence lower TG level and subsequently enhance β-oxidation (to encounter FFA circulation) and therby improve insulin sensitivity (Rhee et al., 2015). It protect β cell from apoptosis (via AMPK pathway) and enhance insulin secretion (Cheng, Liang, & Li, 2013). Studies have shown that Ginkgo biloba could also exert renoprotective and nephroprotective action in diabetic patients (Wu, 2017).

A first clinical trial carried out with ingestion of Ginkgo biloba (EGb761-120 mg for 3 months) in T2DM, non-diabetic or pre-diabetic patients did not show any significant changes at either low or high insulin infusion rate or insulin resistance (Kudolo et al., 2006). Type 2 patients received Ginkgo biloba for 18 months showed better glycemic control (lowering fasting blood glucose; FBG and glycosylated hemoglobin; HbA1c) and psychological state than green tea or placebo (Lasaite, Spadiene, Savickiene, Skesters, & Silova, 2014). However, recently Aziz et al. (2018), inferred that supplementation of Ginkgo biloba extract (120 mg/day for 90 days) in type 2 diabetic patients currently under metformin (standard hypoglycemic drug) can significantly decrease the levels of blood fasting glucose, insulin, HbA1c,

Table 1
Epitomizes the types of synthetic glucose-lowering or hypoglycemic drugs and its mechanism with adverse effects.
Adopted from Tanveer et al. (2017) and Kaur et al. (2017).

<table>
<thead>
<tr>
<th>Hypoglycemic drugs</th>
<th>Mechanism</th>
<th>Adverse effects</th>
</tr>
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<tbody>
<tr>
<td>Sulfonylureas (Glibenclamide, Glimepiride, Glipizide, Tolbutamide)</td>
<td>Stimulate β cells by binding with ATP-dependent K⁺ (K⁺ATP) and inhibit the K⁺ outflow and results in increased insulin secretion (insulin secretagogues).</td>
<td>Weight loss, hypoglycemia, hepatitis</td>
</tr>
<tr>
<td>Non-Sulfonylureas (Meglitinides-Nateglinide, repaglinide)</td>
<td>Increase insulin secretion (acute phase drug) by closing K⁺ channel and opening Ca²⁺ channel.</td>
<td>Increase weight gain, hypoglycemia</td>
</tr>
<tr>
<td>Biguanide (Pioglitazone, Buformin, and Metformin)</td>
<td>Lower the hepatic production of glucose, inhibits gluconeogenesis and increase glucose uptake and thus increase insulin sensitivity and reported to lower lipid profile.</td>
<td>Increase weight gain, renal toxicity, edema, myocardial discomfort.</td>
</tr>
<tr>
<td>Thiazolidinediones (TZDs; - Rosiglitazone, pioglitazone)</td>
<td>Act as PPARγ agonist and upregulate insulin-sensitive genes and thereby lower insulin sensitivity and enhance insulin function.</td>
<td>Renal and cardiac dysfunction, hypoglycemia.</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors (Acrobose, Miglitinol, Voglibose, Pycnogenol)</td>
<td>Slow down the glucose absorption by inhibiting intestinal α-glucosidase, also pancreatic α-amylase.</td>
<td>Increase body weight, GI discomfort, lactic acidosis.</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 (DPP-4) inhibitors (Alogliptin, Sitagliptin, vildagliptin)</td>
<td>Slow down the glucose absorption by inhibiting intestinal α-glucosidase, also pancreatic α-amylase.</td>
<td>Urinary tract infection (UTI), GI discomfort, and pancreatitis</td>
</tr>
<tr>
<td>Sodium-glucose-cotransporter type-2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin)</td>
<td>Improve GLP-1 concentration and thus improve glucose dependent insulin secretion.</td>
<td>Mild weight loss, UTI, genetical infection.</td>
</tr>
<tr>
<td>Insulin (oral; IP or IM)</td>
<td>Improve glucose homeostasis by increasing renal glucose secretion (block the re-uptake of glucose in renal tubules). As oral or injection form, increase glucose uptake and thus lower blood glucose level.</td>
<td>Insulin resistance, painful (chronic usage).</td>
</tr>
</tbody>
</table>

Fig. 1. Represent the anti-diabetic activity (brief mechanism) of various functional foods and herbs in organ specific manner.
BMI and hence the authors suggest that *Ginkgo biloba* can be recommended with metformin in the management of T2DM (adjuvant therapy).

### 3.1.2. Ginseng

*Ginseng* is a slow-growing perennial herb with fleshy roots belonging to Araliaceae family and usually refer to *Panax* species (genus). *Ginseng* can also be classified as function food, but in this review paper, we included Ginseng in the herbal section. Several types of *Panax* genus are reported to show hypoglycemic activity, some of them are *Panax ginseng* C.A. Meyer (Korean red ginseng or Asian or Chinese ginseng), *Panax quinqufolius* L. (American ginseng). The roots (rhizome) are major parts of ginseng with various biological properties. The major active components of *ginseng* are Ginsenoside Rb1/2/c/d/e/f and g1, panaxadiol, protopanaxadiol, compound K (Governa et al., 2018; Nuri, Yee, Gupta, Khan, & Ming, 2016). Ginseng (King of herb) has been used for many years to treat fatigue, aging, depression, gastric ulcer, impotence and hemorrhage (Mucalo et al., 2012). Scientific data also indicate that ginseng shows numerous pharmacological properties including anti-oxidant, anti-inflammatory, hypolipidemic, hypoglycemic, anti-microbial, anti-stress and anti-cancerous activities as well as neuroprotective, cardioprotective and hepatoprotective properties (Bang, Kwak, Ahn, Shin, & Lee, 2014; Nuri et al., 2016).

Anti-hyperglycemic mechanism of ginseng (effectively inhibiting PTP1B via PPAR) and positively regulate various insulin signaling pathway (IRS-AMPK, PI3K/Akt, glycogen synthase kinase 3 beta; GSK-3β) to regulate carbohydrate (increase glucose uptake, glycogen synthesis, inhibit glucoseogenesis via inhibiting Forehead ox protein 1; FOXO-1, impairs intestinal glucose absorption) and lipid metabolism (increase β-oxidation, decrease circulating FFA and LDL-c) as well as act as a potent antioxidant, anti-inflammatory and thus reverse the impaired glucose tolerance or insulin resistance (Gu, Xu, Xu, & Yang, 2016; Mucalo et al., 2012; Wang, Wang, & Chan, 2013). Another study indicated that administration of ginseng could protect the β cells from apoptosis as well as enhance incretin effect (increase GLP/GIP hormone secretion) and thereby increase the production of insulin (Chung, Choi, & Park, 2001).

Bang et al. (2014) demonstrated that T2DM patients supplemented with 5 g of Korean red *ginseng* for 12 weeks displayed a significant reduction in the levels of FBG, OGTT (AUC) as well as decreased the concentrations of serum insulin, C-peptide and thus confirms its hypoglycemic property. A systemic and meta-analysis performed by Gui et al. (2016) evaluated data derived from 8 different clinical trial and reported that ginseng supplementation (0.96–13.6 g/day) for 4–20 weeks can significantly improve (lower) fasting blood glucose, postprandial blood glucose, HbA1c and insulin resistance (Guo, Xu, Xu, & Yang, 2016; Mucalo et al., 2012; Bang et al., 2014; Wang, & Chan, 2013). Another study indicated that administration of ginseng could protect the β cells from apoptosis as well as enhance incretin effect (increase GLP/GIP hormone secretion) and thereby increase the production of insulin (Chung, Choi, & Park, 2001).

A clinical trial conducted by Zhou, Zhang, Yu, and Zou (2007), confirmed the hypoglycemic activity of Radix Astragali (*A. membranaceus*) as it considerably reduced the fasting blood glucose, Hba1c and improve the insulin resistance as well as increased the concentration of adiponectin in T2DM patients. In another trial, treatment with *Astragalus* significantly lowered the fasting blood glucose, postprandial blood glucose, insulin and inflammatory markers like c reactive protein (CRP), tumor necrosis factor alpha (TNF-α) with improving insulin sensitivity (HOMA-IR) than the control group (Fang, 2013). A meta-analysis performed by pooling 13 clinical trial data and concluded that treatment with either Astragalus injection (AI) or Astragalus aqueous decoction (AAD) in T2DM patients by comparing control group inferred that Astragalus could be recommended as adjuvant therapy for managing T2DM by reducing FBG, Hba1c, PPG and HOMA-IR (Tian et al., 2016). Furthermore, Astragalus is one of the major herb of Tianqi (Lian et al., 2014) and JQ-B (Liu, Liu, et al., 2017) Chinese herbal formula. Results of several clinical trials conducted in pre-diabetic and impaired glucose tolerance (IGT) patients have reported that treatment with Tianqi herbal capsule (5 capsules/day orally) for 12–24 weeks with modified lifestyle pattern could decrease FBG and thus reduce the risk of progression to type 2 diabetes mellitus (Gao et al., 2013; Lian et al., 2014). Collectively, *Astragalus* individually or in combination could significantly improve glycemic control in the various model including clinical trial and hence *Astragalus* can be highly recommended for managing T2DM as an adjuvant therapy along with conventional treatment.

### 3.1.4. Gymnema sylvestre

*Gymnema sylvestre* is a perennial woody vine belonging to family Asclepiadaceae (Apocynaceae). It has been used in folk medicine to treat asthma, urinary infection, constipation, and anti-diabetic (Saneja, Sharma, Aneja, & Pahwa, 2010). *Gymnema sylvestre* (G. sylvestre) leaves are rich in various active phytocomponents like gymnemic acid (I-VI-reported to trigger sweet taste), gurmarin and triterpenoid saponins (gymnemosides A-F and W, Conduritol-A) (Wang et al., 2013). Researchers have well documented that *G. sylvestre* possesses potent antioxidant, anti-inflammatory, anti-helminthic, hypolipidemic and anti-obesity activities (Pothuraju, Sharma, Chagalamarri, Jangra, & Kumar Kavadi, 2014; Saneja et al., 2010).

Animal and cell culture studies have indicated that treatment with *G. sylvestre* could exert hypoglycemic effects through lowering intestinal glucose absorption (inhibiting α-amylase and glucosidase/ SGLT1), improving glucose uptake (muscle-GLUT4 via Akt/PI3K) and favour glycolysis and glycogenesis as well as supress glucoseogenesis process. Also, stimulate insulin secretion (via PPARγ activation-β cell proliferation/regeneration and protect β cell from apoptosis),

*G. sylvestre* exhibits hypoglycemic or anti-diabetic activity by positively modulating P38/Akt and AMPK signaling pathway by increasing glucose uptake (increased GLUT4 translocation), preserve β-cells function (anti-apoptotic activity) and thus increase insulin secretion as well as improve insulin sensitivity (Kai, Michela, Antonio, & Annamaria, 2015; Liu, Ma, et al., 2017). Another study conducted with administration of 10 mg/kg of formononetin or Biochanin A (active component of *A. membranaceus*) in STZ induced diabetic rats showed decreased the activities of glucogenesis enzymes and enhance glycogen synthesis via AMPK signaling pathway and thus improve glycemic control (Oza & Kulkarni, 2018). Wu et al. (2005), reported that polysaccharides of *Astragalus membranaceus* could considerably inhibit PTP1B and thus modulate various signaling pathway to showcase its anti-diabetic activity. A combination of *Astragalus membranaceus* and *Euonymus alatus* (Qijian Heji; 3:1 ratio) could considerably lower the blood glucose level in type 2 diabetic knock-out mice model by modulating estrogen receptor and renin expression (Chen et al., 2016).
antagonistic effect on somatotropin and corticosteroid hormone (trigger hypoglycaemia) as well as inhibit excess of protein glycosylation (Leach, 2007; Pothuraju et al., 2014). To concord the above-mentioned possible mechanism few clinical studies are conducted with G. sylvestre. Recently, Shenoy, Prashanth, and Manonmani (2018) demonstrated that triterpene glycoside from G. sylvestre showed better insulin secretion than standard anti-DM drug like glibenclamide via enhancing GLUT-2 expression.

A clinical trial carried out by Baskaran, Ahamath, Shanmugasundaram, and Shanmugasundaram (1990) demonstrated that supplementation of Gymnema sylvestre (GS4) leaves extract in T2DM patients showed a significant decrease in blood glucose level, HbA1c as well as considerably increase the levels of insulin and thus maintain glucose homeostasis. Based on the previous (pre-clinical and clinical studies) FDA has approved G. sylvestre as a supplement to promote health status and hence sold under several brands as Beta Fast GXR, Natrol, Pro Beta and Nature’s way. Intake of commercial G. sylvestre leaf extract (Beta Fast GXR) tablet for 90 days (2 tablets/day) markedly improved glycemic control in T2DM patients by lowering blood glucose (FBG and PPG) and glycosylated hemoglobin level (Joffe & Freed, 2001). An open-label clinical trial carried out by Kumar, Mani, and Mani (2010), concluded that supplementation of 500 mg of G. sylvestre leaf extract with other herbs considerably reduced blood glucose level (FBG/PPG), HbA1c and lipid profile in T2DM patients. Type 2 diabetes mellitus patients treated with high molecular weight G. sylvestre leaf extract (OSA capsule) for 6 days exhibits hypoglycemic effect by reducing blood glucose level as well as increase insulin and C-peptide levels (Al-Romaiyan et al., 2010). Both preclinical and clinical studies have confirmed the anti-hyperglycemic activity of G. sylvestre and hence can be used along with a conventional hypoglycemic drug to manage T2DM.

3.2. Functional foods for treating DM

Functional foods are defined as traditional food (conventional food) or food derived product which can be fortified or modified (enriched) to enhance its nutritive value and thereby improving physiological health status (Santini, Tenore, & Novellino, 2017; Shahidi, 2012). Whereas, nutraceuticals are as a whole food product or part of food (bioactive components from plant or animal source) which could be used as supplements or medicine (pills/capsule) to render various health promoting function in addition to its nutritional value (Dalilu, Santini, & Novellino, 2019; Santini & Novellino, 2018). Copious evidence has shown that functional foods play a vital role in the management of T2DM by improving health status in both animal and human setting (Alkhatib et al., 2017; Bahadoran, Mirmiran, & Azizi, 2013; Mirmiran et al., 2014). However, in this current contribution authors focus on popular functional foods and herbs (nutraceuticals) with positive results in both preclinical and clinical studies.

3.2.1. Aloe vera

Aloe vera (A. vera) is a succulent plant grown in tropical and subtropical regions which belongs to family Asphodelaceae/Xanthorrhoeaceae. A. vera gel (from leaves) are used worldwide for its soothing, healing and rejuvenating properties. It is rich in various macro-molecules (carbohydrates, protein) and micro-molecules (minerals, vitamins), sterols, lignins, salicylic acid and saponins (Surjushe, Vasani, & Saple, 2008). Its major phytoconstituents are Aloeresin A, lophenol, cycloartenol (phytosterols), emodin are responsible for various biological properties especially hypoglycemic (Tanaka et al., 2006). A. vera display a wide spectrum of beneficial actions including antioxidant, anti-inflammatory, anti-hyperlipidemic, hypoglycemic and immunomodulatory properties (Kaur et al., 2017; Pothuraju, Sharma, Onteru, Singh, & Hussain, 2016).

Anti-hyperglycemic mechanism of A. vera includes the positive regulation of various insulin signaling pathway (AMPK, P3K, ERK1/2) and thus lower glucose output and increase glucose input (uptake) as well as inhibit glucose absorption (α-glucosidase) and delay gastric emptying and eventually improve glycemic control (Alnejad-Mofrad, Foadoddini, Safadatjoo, & Shayeesteh, 2015; Huseini, Kianbakht, Hajiaghaee, & Dabaghian, 2012; Pothuraju et al., 2016). Also, it suppresses the obesity induced glucose tolerance via downregulating various inflammatory cytokines and thus improve insulin sensitivity (Shin et al., 2011). Anand et al. (2010), inferred that Aloe emodin-8-O-glucoside (AEG) possess moderate PTPB1 inhibitory activity and could increase insulin secretion (insulin mimetic property). Aloe vera is rich in fibers and starch which helps in promoting gut microbiota (produce SCFAs) and indirectly regulate gut-brain axis and regulate various insulin related signaling pathways (Pothuraju et al., 2016). Moreover, it is prescribed to treat diabetic wound as it exhibits moisturizing property (high water content) and considerably increases collagen production and well as maturation (Beppu et al., 2006).

A randomized, double-blind clinical trial conducted in hyperlipidemic T2DM patients by supplementing with Aloe vera (Capsule-600 mg/day) for 2 months showed reduced fasting blood glucose, HbA1c, TC, LDL-c with altering TG or HDL-c (Huseini et al., 2012). Oral consumption of Aloe vera as a capsule (500 mg) for 8 weeks showed a substantial decrease in FBG, HbA1c, TC, TG, LDL-c with considerable decrease the levels of LDL-c, HbA1c and slightly lowered TC and glucose without any adverse effect. Hence, further trials are needed before recommendation for T2DM patients. Based on the above literature survey it’s clear that all the above-mentioned herbs can be recommended as an adjuvant therapy along with conventional oral hypoglycemic drugs to manage DM. Moreover, FDA has not allowed any specific single herbs alone for managing DM as it’s a dreadful metabolic disease with a high mortality rate (Manukumar, Shiva Kumar, Chandrasekhar, Raghava, & Umesh, 2017; Wang et al., 2013).
improvement in HDL-c in pre-diabetic patients and thus endorse its anti-hyperglycemic and anti-hyperlipidemic properties (Alinejad-Mofrad et al., 2015). A systemic review and meta-analysis executed by Suksoomboon, Poolsup, and Punthanitisarn (2016), demonstrated that aloe vera supplementation significantly lowered the FBG and glycosylated hemoglobin (HbA1c) in T2DM and thus helped in improving glycemic control in type 2 diabetic patients. Based on the above-discussed results, we suggest that aloe vera can be used for managing T2DM patients along with conventional hypoglycemic drugs as well as to combat DM related complication owing to wound healing and laxative properties (Choudhury et al., 2018).

3.2.2. Bitter melon/gourd fruit or Momordica charantia

Bitter melon or Momordica charantia is a sub-tropical climbing plant that bears a bitter fruit (vegetable) and belongs to family Cucurbitaceae. Its fruits, seeds, and leaves are widely used to treat diabetes mellitus owing to its strong bitter taste as well as for common cold, painful menstruation (Governa et al., 2018; Yang et al., 2015). Bitter melon has an array of phytoconstituents, but the major functional ingredients are sterols and triterpenes like charantin, vicine, cucurbitane, momordin II, Kuguaglycoside G, conjugated fatty acids as well as a bioactive protein like polypeptide-p (Njume, Donkor, & McAinch, 2019; Wang et al., 2013). Bitter melon exhibits a wide range of pharmaceutical properties including anti-oxidant, anti-inflammatory, anti-depressant, anti-hyperlipidemic, anti-obesity and hyper-glycemic activities (Chang et al., 2015; Yang et al., 2015).

Momordica charantia shows insulinominmetic property, increase adiponectin secretion, positively regulate the expression of PPARγ (via AMPK pathway) as well as negatively regulate mitogen activated protein kinase (MAPK), JUN-terminal kinase (JNK) and NF-κB signaling pathway and thus mitigate insulin resistance (Chang et al., 2015; Kazem & Davies, 2016; Yang et al., 2015). Inhibit glucose absorption in gut (potent α-glucosidase), preserve β cells (insulin secretagogue) as well as impede gluconeogenesis and glycogenolysis (Governa et al., 2018; Tan, Kha, Parks, & Roach, 2016). In addition, it increases the translocation of GLUT4 and thus increases peripheral glucose uptake via AMPK signaling pathway (Hwang, 2018). In addition, it potentially inhibits PTP1B and thus render the various insulin signaling pathway (Choudhury et al., 2018).

An unblinded randomized clinical trial conducted by John, Cherian, Subhash, and Cherian (2003), demonstrated that intake of 2 tablets of dried bitter gourd (1gm/day) for 4 weeks markedly improved glycemic control by lowering the Fasting Serum Glucose (FSG) and Post-Prandial Serum Glucose (PPSG) in T2DM patients. A clinical trial conducted by Rahman, Khan, Rahman, and Bashir (2015) in type 2 diabetic patients have concluded that intake of bitter melon showed weaker hypoglycemic activity (slight significant reduction in FBG, HbA1c level) but considerably abolishes diabetes-associated cardiovascular markers like blood lipids, atherogenic index, and blood pressure than glibenclamide. A pilot clinical study performed by Selvakumar, Shathirapathy, Jainraj, and Paul (2017), reported that consumption of bitter melon juice could significantly lower mean blood glucose level (acute phase-immediate effect) and thus confirmed its hypoglycemic activity in T2DM patients. Twenty-four type-2 diabetic patients administered with 2000 mg of dried extract of Momordica charantia (bitter melon fruit) for 3 months displayed a substantial decrease in fasting glucose, OGTT, HbA1c, BMI and fat percentage with an increase in insulin as compared with placebo and thereby endorsing its hypoglycemic property (Cortez-Navarrete, Martinez-Abundis, Perez-Rubio, Gonzalez-Ortiz, & Villar, 2018). The above discussed literatures proved the strong anti-hyperglycemic activity of bitter melon in a clinical setting and hence could be urged to consume bitter melon juice along with the conventional anti-diabetic drug for managing T2DM.

3.2.3. Cinnamon family

Cinnamon is a special flavored spice obtained from the bark (inner) of tree belongs to cinnamonum genus like cassia, tamala, verum or zeylanicum. Cinnamon is traditionally used to treat bronchitis, fever, and diabetes (Lee & Balick, 2005). Methylhydroxychalcone polymer-proanthocyanidin (A/B type) and Cinnamaldehyde, cinnamic acid, tannins and volatile oil are the major active principle for various biological properties of cinnamon. Major functional properties of cinnamon are antioxidant (inhibit AGES), anti-inflammatory, anti-tumor, anti-microbial, anti-hyperglycemic and anti-hyperlipidemic activities (Cheng et al., 2012; Ranasinge et al., 2013).

Cinnamomum cassia (Chinese), Cinnamomum verum or Cinnamonum zeylanicum are the major Cinnamon species with anti-diabetic property. Cinnamon can effectively regulate glucose homeostasis by increasing insulin secretion (Insulinotrophic effect) via increased secretion of GLP-1, increase translocation of GLUT4 and thus increase glucose uptake via AMPK signaling pathway, increase PPARγ expression, improve peripheral glucose uptake, inhibit intestinal and pancreatic amylase and glucosidase enzymes and thus reduced the intestinal glucose absorption (Governa et al., 2018; Lakshmi et al., 2009; Medagama, 2015). Increase insulin sensitivity owing to insulin mimetic effect (hydroxycalcone) as well as downregulate the expression of various enzymes involved in glucoseogenesis (Cheng et al., 2012). Cinnamattin B1 from Ceylon cinnamon could activate insulin receptor (increase phosphorylation) and trigger insulin response/sensitivity in adipocytes and myocytes (Taheer, Majid, & Sarmidi, 2012).

Administration of cinnamon extract for 4 months in T2DM patients showed a moderate reduction in the levels of glucose without affecting HbA1c level (Mang et al., 2006). Similarly, Another, clinical trial conducted by Lu et al. (2012), concluded that co-intervention with cinnamon and gliclazide (standard hypoglycemic drug) for 3 months substantially lowered the levels of FBG and HbA1c and thus improve glycemic control in T2DM patients. Anderson et al. (2016), suggested that 2 months of treatment with cinnamon extract can considerably lower the fasting blood glucose level as well as fasting and postprandial insulin concentration which reflected in decreased HOMA-IR and thus improve insulin sensitivity in hyperglycemic patients, but should be prescribed only to non-hepatic DM patients as high amount of coumarin in cinnamon might result in further hepatotoxicity (Choudhury et al., 2018).

3.2.4. Fenugreek or Trigonella foenum-graecum

Fenugreek or Trigonella foenum-graecum is an annual herbaceous legume belongs to Fabaceae. Fenugreek (seed) is one of the spices used for flavoring, coloring and as additive to modify the texture of food. Fenugreek is rich in various nutritious (protein, fat, minerals and vitamins) and was traditionally used to improve body weight, bowel movement as well as to treat digestive problems (Basch, Ulbricht, Kuo, Szapary, & Smith, 2003). The primary chemical constituents of fenugreek are 4-hydroxyisoeucine, trigonelline, furostanol saponins (pro-todioscin), diosgenin (alkaloid) and fibers (insoluble and soluble) (Srinivasan, 2006). Scientist has found that fenugreek could display various range of therapeutic actions including anti-cancer, anti-dietetic, antioxidant, anti-inflammatory and anti-hyperlipidemic (Bahnani, Shirzad, Mirhosseini, Mesripour, & Rafig, 2016; Roberts, 2011).

Possible anti-hyperglycemic of fenugreek- It possess insulin secre-tagogue activity, improve insulin receptor sensitivity (insulin sensitizer) and would inhibit α-amylase, sucrase, α-glicosidase (due to fibers) as well as delay gastric emptying to impair intestinal glucose absorption (El-Soud, Khalil, Hussein, Oraby, & Farrag, 2007). Moreover, fenugreek is reported to inhibit hepatic gluconeogenesis, glycogenesis and protect β cells from apoptosis (regeneration of β cells via upregulating PPARγ) as well as increase GLUT 4 production and translocation thus increase insulin-dependent glucose uptake (peripheral tissues) via upregulating AMPK and PI3K dependent signaling molecules (Bawadi, Maghaydah,
Wang (2017), concluded that consumption of garlic extract (allicin) for therapeutic actions such as antioxidant, anti-fatigue, stress (anti-depressant). The garlic display a broad spectrum of carbohydrate metabolism and reducing pain (analgesic), muscle fatigue, stress (anti-depressant). The garlic display a broad spectrum of therapeutic actions such as antioxidant, anti-inflammatory, anti-obesity, hypolipidemic, anti-hyperglycemia (anti-diabetic), anti-atherosclerotic and anti-coagulant activities (Hosseini & Hosseinzadeh, 2015; Younas & Hussain, 2014). Those above mentioned beneficial activities are due to the presence of various functionally active phyto-components such as alliin, allicin, diallyl disulfide, diallyl trisulfide, diallyl sulfide, S-allyl cysteine sulfoxide, ajene and allyl mercaptan (Volatile sulfur compounds) (Yun et al., 2014).

Ample amount of studies indicated the anti-diabetic effect of garlic (extract or oil-allicin) through acting as insulin secretagogue or sparing insulin effect (Liu, Sheen, & Li, 2007; Padiya & Banerjee, 2013), inhibit glucose absorption (α glucosidase) and transportation as well as impede gluconeogenesis as well as increase glucose utilization by upregulating the enzymes involved in glycolysis and glycogenesis (Choudhury et al., 2018; Younas & Hussain, 2014). Also, increase glucose uptake by increasing GLUT 4 production through Akt/P13K pathway and thereby increase insulin sensitivity (Liu et al., 2007). Furthermore, it shows better anti-glycation and improves endothelial, hepatic and renal functions (Ahmad & Ahmed, 2006).

Randomized, double-blind clinical trial conducted by Sobenin et al. (2008), reported that treatment with garlic powder tablet (allicor) for 4 weeks significantly lowered the fasting blood glucose level, serum triglyceride and fructosamine in T2DM subjects and therefore recommended to alleviate cardiovascular and glycemic risk. Another, 24-week clinical trial also demonstrated that supplementation with high dose (1500 mg/kg) of garlic considerably suppresses the levels of blood glucose and HbA1c than metformin in T2DM (Ashraf, Khan, & Ashraf, 2011). Few clinical trials also conducted with the combination of garlic extract with standard oral anti-diabetic drug also showed the positive effect by improving insulin resistance and lowering cardiovascular risk (Chhatwal, Sharma, Sharma, & Khurana, 2017; Sobenin et al., 2008). A meta-analysis conducted by Wang, Zhang, Lan, and Wang (2017), concluded that consumption of garlic extract (allicin) for 12–24 weeks would significantly lower the blood glucose and lipid profile (except HDL) and hence used for management of T2DM and its related complications. Thus, supplementation of garlic could considerably improve the glycemic control in T2DM patient and can be recommended as an adjuvant therapy along with conventional anti-hyperglycemic drugs.

3.2.6. Ginger or Zingiber officinale

Zingiber officinale (Its rhizome or root is called as ginger) is flowering plant belongs to family Zingiberaceae. Ginger is a popular spice and used commonly in food to give flavor in all type of cuisine. It has been used for many centuries for treating various ailments like a headache, pain, cold, gastric ulcer (Haniadka et al., 2013). It exhibits many biological properties including antioxidant, anti-inflammatory, anti-hyperlipidemic, anti-obesity, anti-cancer, anti-obesity, and anti-diabetic hence it is considered as functional food. Zingerone, shogaol, gingerols (volatile oils) are the main phytocomponents of ginger that are the response to various biological activities especially hypoglycemic (Lindstedt, 2018; Wang, Ke, Bao, Hu, & Chen, 2017).

Ginger can directly or indirectly regulate various insulin signaling pathway (AMPK, Akt) related to insulin sensitivity, enhance glucose uptake-increasing translocation of glucose transporter GLUT4, protect β cells (anti-apoptotic property) and increase regeneration as well as act as a potent antioxidant, anti-inflammatory, anti-thrombotic and hypolipidemic (lower circulating lipid levels) properties and thus improve glycemic control (Bi, Lim, & Henry, 2017; Lindstedt, 2018). In addition, it regulates insulin release/action (insulinotropic activity) and inhibits α-amylase and α-glucosidase enzyme synthesis as well as inhibit enzymes related to gluconeogenesis and glycogenolysis (Beidokhti & Jäger, 2017; Jafarnejad et al., 2017). Furthermore, ginger can protect against various diabetic complications like diabetic retinopathy, nephropathy, neuropathy and hepatic damage (Li, Tran, Duke, & Roufogalis, 2012).

Consumption of ginger (1600 mg/day) for 12 weeks substantially lowered the fasting blood glucose, insulin HbA1c, HOMA-IR, TC and inflammatory markers (CRP, PGE2) as compared with wheat flour placebo in type 2 diabetes mellitus patient (Arablou et al., 2014). Shidfar et al. (2015), reported that consumption of 3 g of ginger for 3 months significantly improved the glycemic indices by lowering serum glucose, HbA1c, insulin levels in T2DM patients. A systemic and meta-analysis combining seven RCTs with T2DM/hyperlipidemia subjects conducted by Jafarnejad et al. (2017), demonstrated that supplementation of ginger significantly lowered the blood glucose and lipid profile levels. Ginger not only reported to attenuate hyperglycemia but also recommended to combat various metabolic syndrome, and it would be beneficial to lower different diabetic related complication as well.

3.2.7. Turmeric or Curcuma longa

Curcuma longa or turmeric is a favorite tropical spice used for flavoring and coloring food especially in Asia. Turmeric has been used in Chinese and India cuisine for many years due to its medicinal properties including an anti-stress, anti-depressant, anti-microbial and derma-protective activity (Amalraj, Pius, Gopi, & Gopi, 2017). The major active components of turmeric are Curcuminoids (Curcumin, desmethoxycurcumin, and Turmerin), cuminol which are responsible for various therapeutic properties like antioxidant, anti-inflammatory, anti-apoptotic, anti-hyperlipidemic, anti-obesity, anti-atherosclerotic, anti-cancer and anti-diabetic (Lobo, Prabhu, Shirwaikar, & Shirwaikar, 2009; Mohankumar & McFarlane, 2011).

Turmeric is well documented for its anti-diabetic activity (improve glycemic control) by acting as anti-AGEs agent, an insulin secretagogue/insulinotropic activity (improve insulin secretion), and regulate various insulin signaling pathway (AMPK, Akt) thus enhance insulin secretion and transportation (Ghorbani, Hekmatdoost, & Mirrman, 2014; Mohankumar & McFarlane, 2011). Turmeric is reported to inhibit β cell apoptosis and enhance glycolysis and β oxidation. It acts as a natural PPAR-γ agonist as well as down regulate the protein expression of various proteins involved in MAPK signaling pathway (Bi et al., 2017; Kim et al., 2010). Furthermore, turmeric is reported to abolish insulin resistance and inhibit glucose reabsorption as well as inhibit α-
glucosidase and α-amylase (Lekshmi, Arimboor, Indulekha, & Nirmala Menon, 2012).

A marked reduction in the levels of fasting blood glucose, HOMA-IR, HbA1c as well as serum triglyceride, free fatty acids (promote fatty acid oxidation) were noted in T2DM patients supplemented with curcuminoids for 3 months (Na et al., 2013). Type-2 diabetic patients supplemented with nano-curcumin for 3 months significantly lowered the mean concentration of FBG, HbA1c, and TG as compared to placebo (Rahimi et al., 2016). A systemic review and meta-analysis performed by de Melo, dos Santos, and Bueno (2018) including 11 randomized controlled studies have concluded that supplementation of curcumin or and curcuminoids (turmeric extract) could significantly lower fasting blood glucose level and HbA1c percentage in diabetes patients. Collectively, turmeric and its phytocomponents are suggest to treat against T2DM and its related complications.

### 3.2.8. *Camellia sinensis* or green tea

Green tea is made from the leaves of *Camellia sinensis* (by mild oxidation) which belongs to the Theaceae family. Green tea is the highly consumed beverage next to water globally, and hence high attention was shown by many researchers (Venkatakrishnan et al., 2018). Several authors confirmed that the catechins especially epigallocatechin-3-gallate (EGCG) is the major contributor for most of the biological properties including antioxidant, anti-inflammatory, anti-obesity (thermogenic), anti-cancer, anti-diabetic as well as cardioprotective, neuroprotective properties (Chiu, Lin, Shen, Venkatakrishnan, & Wang, 2016; Zhang et al., 2017).

Catechins/polyphenols of green tea can positively regulate PPARα and PPARγ as well as act as potent antioxidant/glycation (anti-AGEs), anti-inflammatory, hypolipidemic, anti-obesity as well as regulate various insulin signaling pathway (AMPK and Akt/Pi3K via nuclear factor erythroid 2 related factor 2; Nrf2) thus increase insulin secretion, insulin-mimetic action, decrease insulin resistance/tolerance (increasing GLP-1) and decrease gluconeogenesis as well as inhibit sodium dependent glucose transporters (SGLT-1/2) (Wolfrahm et al., 2006; Zhang et al., 2017). Cao et al. (2007) hinted that green tea extract (polyphenol-EGCG) could regulate the genes involved in glucose uptake (GLUT-2 in liver and adipose tissue and GLUT-4 in muscle) as well as phospholipate various downstream insulin signaling pathway including PI3K/Akt, AMPK. Furthermore, inhibit intestinal glucose absorption (α glucosidase) and reduce β cell damage as well as protect endothelium (vascular), renal and hepatic tissue from DM related damage (Dabur, Sharma, & Mittal, 2018).

A clinical trial conducted by Fukino et al. (2008) also demonstrated that consumption of green tea extract for 8 weeks could significantly lower the levels of HbA1c in subjects with glucose abnormalities. Furthermore, Liu et al. (2014) concluded that consumption of green tea extracts markedly improved (within the group) the insulin resistance and increased glucagon like peptide-1 (GLP-1) production in T2DM patients. A review conducted by Lau et al. (2016), concluded that intake of green tea catechins (GTCs) could lower cardiovascular markers like lipid profile (TC, TG, LDL-c), BMI, blood pressure (SBP, DBP). However, few studies have shown that intake of green tea or its extract did not show marked impact on fasting glucose, insulin and HbA1c levels in T2DM patients (Hua et al., 2011; Wang et al., 2014). Similarly, a meta-analysis performed by Yu, Song, Perry, Penfold, and Cooper (2017) analyzed data derived from 6 RCTs and reported that treatment with green tea or green tea extract did not show significant changes in the levels of fasting glucose, insulin, HbA1c and HOMA-IR in pre-diabetes and T2DM patients. However, the authors indicated that only small number of studies are included (n = 6) with varying quality (less sample size/short trial) and concluded that further studies are needed with many trials (studies) with longer duration/follow-up and a large number of subjects. Overall, green tea could be consumed by T2DM patients to lower DM related complication as well as moderately improve glycemic control.

### 3.2.9. Soybean or glycine max

Soybean is a popular annual legume of the pea family (Fabaceae). The edible seeds (soybean) is used as food with various pharmaceutical properties including antioxidant, anti-inflammatory, anti-estrogen (thermogenic) hypolipidemic activities and hence considered as a functional food (Tidke, Ramakrishna, Kiran, Kosturkova, & Ravishankar, 2015). Major functional constituents of soybeans are soy isoflavones (Genistein and Daidzein), peptides (soy proteins-11S; 7S globulin), phytoestrogen and phytoalexins (Glyceollin I-IV) (Chang et al., 2013; Park et al., 2010).

Soy bean (isoflavones) are reported to improve insulin secretion and glucose uptake (GLUT4) by increasing β-cell count/proliferation (inhibit insulin resistance), inhibit the intestinal α-glucosidase/αamylase as well as promote GLP-1 secretion and exert estrogenic activity (Gilbert & Liu, 2013) as well as regulate various insulin signaling pathway-ERK1/2, Akt, AMPK (upregulation), induce PPARα (Chang et al., 2013; Cho et al., 2010) and thus alter carbohydrate and lipid metabolism. Moreover, it supress the activity of various enzymes involved in gluconeogenesis and enhance the hepatic lipogenesis and β-oxidation (Dabur et al., 2018). Also, reported to abolish various DM related complications like diabetic retinopathy, nephropathy (Beidokhi & Jäger, 2017).

Intervention with isoflavone of soybeans (100 mg) for one year resulted in improved insulin sensitivity with lowering of cardiovascular risk factors like lipid profile and its ratio’s (TC/HDL-c) in post-menopausal T2DM patients (Curtis et al., 2012). T2DM patient administration with 30 g (66 mg of isoflavones) of soy (SPI) showed better glycemic control by decreasing fasting insulin, glucose levels, glycosylated hemoglobin and HOMA-IR as well as lowered various cardiovascular risk factors (lipid profile, inflammatory markers) than T2DM patient’s administration with only 30 g of soy without isoflavones (SP) and thus demonstrated that isoflavones are the major contributors for maintaining glucose homeostasis (Sathiyapalan, Thatcher, Rigby, Kılıçpatrick, & Atkin, 2015). A meta-analysis performed by Zhang, Zhang, and Chi (2016), revealed that consumption of soy protein (especially long-term) could positively regulate the levels of FBG, insulin, HbA1c, HOMA-IR, blood pressure and lipid profile in T2DM and Metabolic syndrome subjects. However, a systemic review and meta-analysis including few clinical trials highlighted that intake of soy or soy derived proteins did not show a significant effect on glycemic control or indices but slightly lower fasting blood glucose and TG (Li, Ruan, Peng, & Wang, 2018). The above studies proved that soy and its derivatives (active components) consumption could improve glycemic control along with cardiovascular risk and can be used for managing T2DM and its related complications.

### 3.2.10. Polysaturated fatty acids (PUFA)/Omega-3-fatty acids

Omega(ω)-3-fatty (ω-3 FA) acids belong to polysaturated fatty acids (PUFA) and are also classified as essential fatty acids. The major omega-3-fatty acids are ω-linolenic acid (ALA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (Kondo et al., 2014). Omega fatty acids (DHA/EPA) are reported to show numerous biological properties including antioxidant, anti-inflammatory, immunomodulatory, hypolipidemic, anti-obesity, anti-diabetic as well as cardioprotective (improve endothelial function), neuroprotective activities (Belchior et al., 2015; Wong et al., 2010).

Anti-hyperglycemic activity of ω-3 FA includes anti-glycation (anti-AGEs/antioxidant), anti-inflammatory and anti-obesity effect and thereby increasing adiponectin secretion and reduce the insulin sensitivity (Azizi-Soleiman et al., 2013; Iwase, Kamei, & Takeda-Morishita, 2015), improve GLP-1 secretion (Chang et al., 2013). Also, ω-3 FA can upregulate PPAR signaling pathway in skeletal muscle and hepatocytes and thereby modulate the carbohydrate metabolism (decrease gluconeogenesis and increase glycolysis) and lipid metabolism (decrease hepatic lipogenesis and increase β oxidation) in diabetic model to improve glycemic control (Iwase et al., 2015). Moreover, the consumption of fish oil rich in DHA/EPA can significantly improve renal function in...
T2DM patients, and thus it can be recommended against diabetic nephropathy and neuropathy as well as improve endothelia dysfunction (Wong et al., 2010).

A prospective cohort study conducted by Zheng, Huang, Yang, Fu, and Li (2012) concluded that intake of marine n-3 polyunsaturated fatty acid (n-3 PUFA) are inversely associated with the risk of T2DM in Asians. EPA consumed (2 g/day for 2 weeks) T2DM patients showed a significant reduction in the levels of fasting plasma glucose and HbA1c with a slight reduction in HOMA-IR and thus proving the hypoglycemic property of EPA (PUFA) (Sarbolouki et al., 2013). A systemic and meta-analysis of RCTs concluded that administration of n-3 polyunsaturated fatty acid (n-3 PUFA) or omega-3 FA could decrease various inflammatory markers like CRP, TNF-α, and IL-6 in T2DM patients (Lin et al., 2016). Similarly, Azizi-Soleiman et al. (2013) also demonstrated that supplementation of EPA and DHA (1 g/day) considerably lowered the oxidative stress in T2DM subjects. From the above data, it’s clear that omega-3 FA can only help in attenuate DM associated complication but no or mild direct hypoglycemic activity (in a clinical setting-need further studies).

3.2.11. Probiotic and prebiotic

Probiotics are living gut microorganism that is believed to enhance host health benefits. Prebiotics is defined as non-digested food that stimulates the growth of host beneficial bacterial species (probiotics) in the gut (colon) that positively influence the composition of gut microbiota. Probiotics like Lactobacillus and Bifidobacterium spp. (Beneficial bacteria’s) are commonly used in various commercial food products to enhance the composition of gut microbiota (Chiu et al., 2017). Probiotics/prebiotics favor various health-promoting properties like immune modulation, anti-cancer, antioxidant, anti-inflammatory, anti-hyperlipidemic, anti-atherosclerotic and anti-diabetic (Iqbal et al., 2014; Kellow, Coughlan, & Reid, 2014). Moreover, probiotic can help to produce various short chain fatty acid (SCFA; fermentation end products) like acetate, butyrate, propionate. The SCFA plays a vital role in regulating many processes like energy metabolism (the energy source for epithelium/enterocytes), regulate lipid and carbohydrate metabolism (lower circulating FFA and glucose), decrease pH, increase insulin sensitivity (Chiu et al., 2017; Tonucci, Santos, & Ferreira, 2015).

Prebiotics (SCFA) could possibly modulate gut microbiota, which in turn activate CNS (gut-brain axis) and enhance the production of GLP-1, gastric inhibitory proteins (GIP), cholecystokinin (CCK) and peptide YY (PYY) and subsequently induced insulin secretion and glucose uptake (GLUT-4 via AMPK) in peripheral organs especially muscle. Also, enhance the glycogenesis by absorbing increased blood glucose (Ostadrahimi et al., 2015; Patterson et al., 2016; Tonucci et al., 2015). Moreover, it has been well documented that pre/pro-biotics trigger β cell proliferation and leptin production as well as inhibit β cell apoptosis (Gomes, Bueno, de Souza, & Mota, 2014).

Ejtahed et al. (2012) conducted a randomized, double-blind clinical trial consisting of 64 T2DM patients and supplemented with probiotic yogurt (Lactobacillus-La5, Bifidobacterium-Bb12) for 6 weeks. At the end of the intervention, the yogurt consumed patients showed decreased fasting blood glucose, HbA1c levels with increased antioxidant activities and thus proving that yogurt (probiotics) intake can positively regulate glucose homeostasis. Consumption of multispecies probiotic for 8 weeks in T2DM patients attenuated the raised glucose level as well as oxidative stress and inflammatory response as compared to the placebo group (Asemi, Zare, Shakeri, Sabihi, & Esmaillzadeh, 2013). Fasting blood glucose level and HbA1c percentage were significantly reduced upon consumption of probiotic fermented milk (rich in Lacto-bacillus and Bifidobacteria spp) without altering lipid profile in T2DM patients (Ostadrahimi et al., 2015). Recently, Nikbakht et al. (2018) conducted a systemic and meta-analysis controlled trial and concluded that supplementation of both probiotic (multispecies) or symbiotic would significantly lower the blood glucose level in hyperglycemic subjects via positively regulating gut microbiota. Taking together, pro/pre-biotics can positively modulate gut microbiota and enhance SCFA and lower hyperglycemia via Gut-Brain axis, suppressing inflammation, oxidative stress and altered carbohydrate and lipid metabolism.

3.2.12. Whole grains

Whole grains (WG- represent bran, germ, endosperm) including Wheat, barley, oats, rice, and rye contains high levels of non-digestible polysaccharides (NDPs) like soluble/insoluble fibers, β glucans, inulin, and resistant starch. These NDPs aids in bowel movement, lower constipation by giving bulkiness to feces, increase the assimilation of minerals in the gut and enhance fat oxidation and thus exhibit hypolipidemic property (Meeu & Xu, 2018). The NDPs are fermented by bacteria’s (probiotic) in gut microbiota (colon) and involved in SCFA (as mentioned in pre and probiotic section). NDPs are reported to combat various metabolic syndromes like CVDS, obesity and DM (Ye, Chacko, Chou, Kugizaki, & Liu, 2012) by enhancing oxidative status and abolish the inflammatory response and plasma lipid levels (Liao et al., 2019).

Whole grains (NDPs) are reported to modulate the gut microbiota (increase beneficial bacterial count) thereby increasing the secretion of GLP-1 and decrease ghrelin production, increase leptin production (thus increase insulin secretion and glucose uptake as indicated in previous probiotic section). β glucans are reported to positively regulate Akt/P3K signaling pathway to lower glucose level (Chen & Raymond, 2008). Inulin could significantly suppress JNK and MAPK signaling pathway and thereby improve insulin sensitivity (Ning et al., 2017). Also, shown to decrease intestinal cholesterol absorption by inhibiting α glucosidase as well as delay gastric emptying (Rosén, Östman, & Björck, 2011; Dainty et al., 2016).

Supplementation with high-performance inulin in T2DM women for 8 weeks caused a significant decrease in FBG, HbA1c and lipid profiles as compared with control (maltodextrin) and can be used to improve glycemic status in T2DM patients (Dehghan, Gargari, & Agharjafarabadi, 2013). Lin, Chang, Wu, Peng, and Chung (2015), concluded that consumption of resistant starch formula (PBR-R-2003) could considerably reduce postprandial glucose level without causing hypoglycemia in T2DM patients. Consumption of different resistance starch bagel could improve glycemic control (insulin sensitivity) by lowering the fasting insulin and HOMA-IR levels in pre-type 2 diabetes mellitus patients (Dainty et al., 2016). A meta-analysis of RCT was performed by Shen et al. (2016) including 4 trials and reported that intake of β glucan (oat) significantly reduced plasma glucose level and HbA1c without altering fasting plasma insulin level in T2DM patients.

As indicated before, some clinical trials have been conducted by combining several functional foods to combat DM and its related complications (Kazeem & Davies, 2016; Wang et al., 2013). In addition, few clinical trials also carried out by combining functional foodstuff with conventional (standard) anti-hyperglycemic agents. Nevertheless, some phytocomponents (nutraceuticals) in the food materials might interact with the conventional hypoglycemic drug (drug-nutrient interaction) masking the efficacy of the conventional hypoglycemic drug (Izzo, 2012; May & Schindler, 2016). For instance, the phytocomponents of okra (functional food) are reported to inhibit metformin absorption (Khutan, Rahman, Biswas, & Islam, 2011). Hence, the efficacy and safety are the major criteria to look for any combination anti-DM drugs before intervention.

The strength of the present contribution is the involvement of various popular functional foods and herbs (phytomedicine) with anti-diabetic activity particularly focused on T2DM with special reference to clinical trials (meta-analysis) and its proposed mechanism. The schematic representation of anti-diabetic activity of various herbs and functional foods and its underpinning mechanism are depicted in Fig. 2. This contribution (review) would open the gate for many researchers/pharmacists on developing a novel functional food or nutraceuticals with the potent anti-diabetic property with less adverse effect. Secondly, the common people (reader) can also get updated information.
about current DM treatment regimen as well as alternative medicine (natural) for treating DM without serious adverse effect. Some of the limitations of this contribution are focusing only on popular Traditional Chinese and Indian herbs and popular functional foods. Also, the authors concentrated only on T2DM in the clinical setting as it’s the primary type of DM (90%).

4. Conclusion/future perspective

This review highlighted the potential of various major glucose-lowering herbs and functional foods concerning clinical trial (especially with the latest meta-analysis) and demonstrated its hypoglycemic mechanism from both in vitro and in vivo studies. Based on the literature (systemic review/meta-analysis) most of the researchers indicated that co-intervention of functional food/herbs (adjunct therapy) with a conventional hypoglycemic drug with modified lifestyle pattern could significantly lower blood glucose level and help to maintain glucose homeostasis as well as abolish associated complications like diabetic nephropathy, neuropathy, and retinopathy. However, more data from human clinical trials are needed to ensure the safety and efficacy of different functional food/herbs with the conventional hypoglycemic drug (holistic/synergetic) especially the dosage/duration/mode of administration are crucial to avoid adverse effect and to improve glycemic control. Near future, the active component which contributes to anti-hyperglycaemic activity (and its underlining mechanism-various signaling pathway in modulating various diabetogenic genes-INSR, HMGA1, PTP-1B) must be revealed to concord the anti-diabetic efficacy and safety.

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Conflict of interest

No conflict of interest to disclose for this review article

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