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REVIEW PAPER

Anti-diabetic potential of selected Indian traditional herbals containing polyphenols as the major ingredient- A preview

R. Arathy[1], G. S. Manoj[2], G. M. Greeshma[3], K. V. Dinesh Babu[4], Bosco Lawarence[5], S. S. Sumyya[6] & K. Murugan[7*]
[1, 2, 3] Department of Botany, Mahatma Gandhi College, Thiruvananthapuram-695004
[4]Department of Chemistry, Government College for Women, Thiruvananthapuram-695014
[5]Government Arts College, Thycaud, Thiruvananthapuram-695014
[6]Department of Botany, SNGS College, Pattambi, Palakkad- 679306
[7]Center for Innovation in Science and Social Action (CISSA), Thiruvananthapuram-695010, Kerala, India
[*]Corresponding Author: harimurukan@gmail.com

Abstract

Many medicinal species function as anti-diabetics due to their active pool of phytochemicals. Plants showing hypoglycemic potential belong commonly to Fabaceae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae and Araliaceae. The most active species are *Allium sativum, Gymnema sylvestre, Citrullus colocynthis, Trigonella foenum-greacum, Momordica charantia* and *Ficus benghalensis*. Biomolecules containing high polyphenol levels can control glucose metabolism by diverse mechanisms like protecting and restoring beta-cell integrity, enhancing insulin releasing potential, and increasing cellular glucose uptake. Blackberries, red grapes, apricots, eggplant, coffee, cocoa and green tea are rich in polyphenols, which may dampen insulin resistance and be a natural substitute for the treatment of diabetes. Many proven reports suggest that polyphenols from various sources stimulate β-cells to secrete insulin and the peripheral response to insulin. The glucose-lowering potential of polyphenols has been evidenced in many acute and chronic models of healthy and diabetic animals. Some polyphenols appear to exert their effects similar to pharmaceutical antidiabetics; thus, more intense clinical trials are needed to fully validate this claim.

Keywords: Medicinal plants, antidiabetic, polyphenols, traditional knowledge, insulin

Introduction

Diabetes mellitus is a complex physiological disorder that has severely affected the human health and quality of life. Salient feature of diabetes is hyperglycemia, which reflects the deterioration in the use of glucose due to a faulty or low response to insulin secretion. It is reported that 25% of the global population is affected by this disorder. Being a multifactorial disease, it requires multiple therapeutic approaches. Type II diabetes or non-insulin-dependent diabetes mellitus, is the most common form of the disease, accounting for 90–95% of cases in which the body does not produce enough insulin or properly use it.

Gathering the information and documentation of native knowledge plays a unique role in scientific research on drug designing. WHO depicts that over 80% of world's population depends on plant resources for their primary healthcare needs. From the aboriginal periods, Indian medicinal plants have served as primary source of medicines for the prevention and treatment of many diseases and disorders. Ethnobotany reflects a complex relationship between herbals, native people and culture and this relationship between plants and human cultures is not limited to the usage of plants for food, clothing and shelter but also includes their use for religious ceremonies, ornamentation and health care. It is estimated that more than 900 species of plants exhibit hypoglycemic properties,

including many common plants, such as bitter gourd.

Synthetic drugs are being used to regulate diabetes along with lifestyle management. However, they are not effective and there are no reports of full recovery from diabetes. Many herbals have been used for the management of diabetes mellitus in diverse traditional practices of medicine such as Ayurveda, Unani, and Homeopathy etc. worldwide as they are potential source of bio-constituents and many of them are known to be preventive and curative against diabetes. Medicinal plants with antihyperglycemic activities are being more desired, owing to minimal side-effects and low cost. Herbals that contain a pool of phytochemicals like glycosides, alkaloids, terpenoids, flavonoids, anthocyanins, carotenoids, etc., are frequently implicated as having antidiabetic effects. This review on the different plant species that have been reported to be effective in diabetes.

Herbalists treat many lifestyle disorders like asthma, eczema, premenstrual syndrome, rheumatoid arthritis, migraine, menopausal symptoms, chronic fatigue, and irritable bowel syndrome, among others. Many Ayurvedic formulations have been used in the treatment of diabetes mellitus from time immemorial. Researchers have made studies in the chemical composition of the antidiabetic medicinal herbs used in Ayurveda. This review deals with work done on Indian medicinal plants with anti-diabetic potential.

Medicinal plants used against diabetes

The biological activities considered are antidiabetic, antihyperglycemic, and hypoglycemic activities as well as α-amylase and α-glucosidase inhibition. The diverse categories of plants used against diabetes are listed below.

1. Plant drugs acting like Insulin/ producing insulin mimic effect

Aegle marmelos, *Momordica charantia*, *Pterocarpus marsupium*, *Sarcopoterium spinosum*

2. Plant drugs increasing Insulin secretion/ release from beta cells

Citrullus colocynthis, *Ficus benghalensis*, *Allium cepa*, *Allium sativum*, *Ocimum sanctum*, *Aloe barbadensis*, *Nigella sativum*

3. Plant drugs with possible action of regeneration/repair of beta cells of islets of Langerhans

Pterocarpus marsupium, *Gymnema sylvestre*, *Elephantopus scaber*

4. Plant drugs which delay glucose absorption from gastrointestinal tract

Caesalpinia bonducella, *Mangifera indica*

5. Plant drugs showing alpha-amylase & alpha-glucosidase inhibitory effects

Tinospora cordifolia, *Aegle marmelos*, *Coccinia indica*, *Ocimum sanctum*

6. Plant drugs modifying glucose utilization

Zingiber officinale, *Azadirachta indica*, *Andrographis paniculata*

The proven anti-diabetic plants comprise 21 plant species (Table-1)

Table 1
List of proven anti-diabetic plant

Sl. No.	Binomial	Family	Mode of action
1	*Acacia arabica*	Leguminosae	Release of insulin from pancreas
2	*Aloe barbadensis*	Liliaceae	Stimulating synthesis and release of insulin
3	*Annona squamosa*	Annonaceae	Increases plasma insulin level
4	*Averrhoa bilimbi*	Oxalidaceae	Increases serum insulin level
5	*Bixa orellana*	Bixaceae	Increases plasma insulin concentration and insulin binding on insulin receptor
6	*Boerhaavia diffusa*	Nyctaginaceae	Increases plasma insulin concentration
7	*Camellia sinensis*	Theaceae	Increases insulin secretion
8	*Capsicum frutescens*	Solanaceae	Increases insulin secretion and reduces insulin binding on the insulin receptor

9	*Cinnamomum zeylanicum*	Lauraceae	Elevation in plasma insulin level
10	*Eucalyptus globulus*	Myrtaceae	Stimulates secretion of insulin
11	*Ficus religiosa*	Moraceae	Increases insulin secretion from clonal pancreatic beta line (BRIN-BD 11)
12	*Hibiscus rosea*	Malvaceae	Initiates release of insulin
13	*Helicteres isora*	Sterculiaceae	Decreases plasma triglyceride level and insulin sensitizing activity
14	*Ipomoea batata*	Convolvulaceae	Reduces insulin resistance and blood glucose level
15	*Olea europia*	Oleaceae	Increases insulin release and peripheral uptake of glucose
16	*Swertia chirayata*	Gentianaceae	Stimulates insulin release from islets
17	*Scoparia dulcis*	Scrophulariaceae	Insulin-secretagogue activity
18	*Tinospora crispa*	Menispermaceae	Anti-hyperglycemic, stimulates insulin release from islets
19	*Urtica dioica*	Urticaceae	Increases insulin secretion
20	*Zingiber officinale*	Zingiberaceae	Beta cell rejuvenation, regeneration and stimulation
21	*Vinca rosea*	Apocynaceae	Increases insulin level and decreases fasting glucose level

Table 2
List of anti-diabetic plants with parts used

Sl. No.	Plants	Part used
1.	*Artemisia pallens, Bidens pilosa, Bixa orellana*	Bark
2.	*Allium cepa, Allium sativum*	Bulb
3.	*Cassia auriculata, Musa sapientum*	Flower
4.	*Carum carvi, Coriandrum sativum, Emblica officinalis, Momordica charantia, Xanthium strumarium*	Fruit
5.	*Annona squamosa, Averrhoa bilimbi, Azadirachta indica, Beta vulgaris, Camellia sinensis, Cassia alata, Eclipta alba, Eucalyptus globulus, Ficus carica, Gymnema sylvestre, Gynura procumbens, Ipomoea aquatica, Mangifera indica, Myrtus communis, Memecylon umbellatum, Morus indica, Ocimum sanctum*	Leaves
6.	*Nelumbo nucifera*	Rhizome
7.	*Glycyrrhiza glabra, Helicteres isora, Pandanus odorus*	Root
8.	*Acacia arabica, Lupinus albus, Luffa aegyptiaca, Lepidium sativum, Mucuna pruriens, Punica granatum*	Seed
9.	*Amaranthus spinosus, Coscinium fenestratum*	Stem
10.	*Ipomoea batatas*	Tuber
11.	*Achyranthus aspera, Aloe vera, Anacardium occidentale, Andrographis paniculata, Capsicum frutescens, Cryptolepis sanguinolenta, Enicostemma littorale, Ficus religiosa*	Entire plant

Table- 2 Narrates the species of plants with its part used by the native people for curing diabetes. Most of the plant species enlisted above had proved for their polyphenols herein as their active ingredient. So, the role of phenols in regulating diabetes is discussed.

Polyphenolics are aromatic phytochemicals having benzene ring with hydroxyl groups and are produced for their protection against biotic and abiotic stress. Generally, polyphenolics can be divided into flavonoids and non-flavonoids groups.

Flavonoids

They are water soluble polyphenols possessing two benzene rings bonded with a short three carbon chain. Chalcone, flavone, flavanol, flavanone, isoflavonoids and anthocyanins are the major flavonoids. The compound is known for anti-inflammatory, antidiabetic, anticancer, neuro-protective and cardiac protective roles. Generally, the compound induces insulin secretion, promotes proliferation of pancreatic β-cells, glucose uptake, and lowers insulin resistance, inflammation and oxidative stress. Major flavones are apigenin, luteolin, chrysine, 7- hydroxyflavone, galangin, fisetin, genistein (isoflavone), gardenin, tangeretin, 8- methoxyflavone, hispidulin, and acacetin. Chemically it is benzopyrans and common in fruits and vegetables. Apigenin is involved in regulating hepatic oxidants, hyperglycemia, hepatic G3Pase and cholesterol in alloxan induced diabetic animals. Fang (2005) proved apigenin inhibited expression of HIF-1α and VEGF via the PI3K/AKT/ p70S6K1 and HDM2/ p53 pathways. Similarly, it inhibited tube formation *in vitro* by endothelial cells, thus critical for tumor angiogenesis and growth, identifying new signaling molecules that mediate this regulation. Luteolin and chrysin regulates maltase and phosphorylation through activation of PPAR-γ and thereby lipogenesis and glycogenesis. Further, they also control NO and ROS levels. Luteolin was reported to raise adiponectin levels and decrease MCP-1 and increase insulin sensitivity in mice models. It also controls insulin resistance due to its anti-inflammatory activities and inhibit NF-κB, iNOS-NO and IKKb/IRS- 1/Akt/eNOS-dependent signaling pathways. Chrysin reduced expression of renal TNF-α, transforming growth factor-beta (TGF-β) and inhibited the nuclear transcription factor-kappa B (NF-κB) activation (Ahad et al., 2014). Galangin of *Alpinia officinarum* was found to regulate/suppress C/EBPα, fatty acid synthase, SREBP-1, and PPAR-γ expression in liver and adipose tissues. Similarly, it controlled inflammatory and oxidative burst by reducing the NF-KB translocation into the nucleus induced in fructose fed animals. (Jung et al., 2014; Choi et al., 2017). Flavone, tangeretin of Citrus fruits was reported to reduce body weight, total cholesterol, blood glucose, adiponectin, leptin, resistin, and pro-inflammatory cytokines i.e., IL-6, and MCP-1 (Zhang et al., 2015; Khan et al., 2016). Isoflavones such as daidzein, genistein, formononetin, biochanin A, cuneatin, luteone, alpinumisoflavone, retusin, tectoridin, and prunetin have been reported from many plant species (Cho et al., 2010; Sun et al., 2016). Genistein of soy isoflavone induced β-cell proliferation, insulin secretion, and estrogen receptor and thereby antiapoptotic, antioxidant potential and tyrosine kinase activity. Further, it induces calmodulin kinase II (CaMK II) and Ca^{2+} signaling resulting in insulin secretion (Hwang et al., 2005; Liu et al., 2006; Behloul et al., 2013; Gupta et al., 2016).

Formononetin, an O-methylated isoflavone of *Astragalus membranaceus* is known for its cardioprotective, anti-inflammatory, and rejuvenate properties (Wang et al., 2014; Chundi et al., 2016). Tectorigenin, tectoridin, irigenin, swertisin and their glucosides from the rhizomes of *Belamcanda chinensis* inhibits aldose reductase, an enzyme that synthesizes sorbitol in diabetics (Lee et al., 2000; Jung et al., 2002; Alonso-Castro et al., 2012).

Flavanols such as kaempferol, myricetin, quercetin, fisetin, rhamnazin and isorhamnetin are dietary components. Quercetin and its glycosides from *Vaccinium vitis-idaea* activate insulin independent AMPK pathway in muscle cells (Eid et al., 2010). Kaempferol of fruits and vegetables displays pharmacologic activities like anti-diabetic, hypolipidemic, anti-cancer, cardio-protective and anti-atherosclerosis (Zhang et al., 2013; Luo et al., 2015; Al-Numair et al., 2015).

Myricetin, the benzo-α-pyrone shows antioxidant property like D-α-tocopherol (Li and Ding 2012; Li et al., 2017). Pentamethyl quercetin a potential antidiabetic agent reduced postprandial glucose and triglyceride levels by reducing insulin resistance, activating AMPK and increasing ACC phosphorylation and GLUT4 abundance (Chen et al., 2011; Li et al., 2013; Xin et al., 2013). Morin proved its role via regulating TNF-α, IL-1β, IL-6 and lipid peroxides levels in animal and cell lines via SphK1/S1P signaling (reduced NF-κB activation and other inflammatory cytokines) (Pashikanti et al., 2010; Ghorbani, 2017).

Flavanols are derivatives of flavanones having 2-phenyl-3,4-dihydro-2H-chromen-3-ol skeleton

existing as monomers or oligomers in fruits, foods, teas, and cocoa. The common examples are catechin, epicatechin, epicatechin gallate, epigallocatechin, epigallocatechin gallate, proanthocyanidins, theaflavins, thearubigins, procyanidin, inulavosin, and dihydromyricetin. Catechin of *Cassia fistula* used in Indian medicine in reducing the blood glucose levels in Streptozotocin-induced diabetic rats (Cho et al., 2007; Shin et al., 2009; Thielecke and Boschmann 2009 and (Daisy et al., 2010). (−)-Epicatechin of cocoa and chocolates from *Pterocarpus marsupium* reported for antidiabetic and insulin mimetic effects via scavenging ROS directly and also by modulating anti-oxidative defense system (Kim et al., 2014; Shay et al., 2015; Cordero-Herrera et al., 2017). Epigallocatechin gallate (EGCG) displays diverse mechanisms in insulin signaling pathways where it affects the IRS2, Akt, FoXO1, PDX-1, mass and functional integrity of mitochondria.

Flavanones are flavans with a 3,4-dihydro-2-aryl-2H-1-benzopyran-4-one skeleton and the common examples are hesperidin, hesperetin, naringin, naringenin, bavachinin, dihydrorobinetin, licoisoflavanone, dihydromyricetin, licoleafol, and pinobanksin. They proved their role as antioxidant, anti-diabetic, lipid-lowering, anti-atherogenic, and anti-inflammatory.

Hesperidin is known for hypoglycemic and hypolipidemic properties through increasing glycolysis and glycogen contents in STZ induced diabetic rats (Mahmoud et al., 2012; Constantin et al., 2014; Agrawal et al., 2014; Umeno et al., 2016). Neohesperidin, another molecule decreases fasting glucose, serum glucose, glycosylated serum protein (GSP), TG, TC, leptin level, liver index and elevated oral glucose tolerance and insulin sensitivity and decreased insulin resistance in KK-A(y) diabetic animals. It inhibits the stearoyl-CoA desaturase 1 (SCD-1) and fatty acid synthase (FAS) gene expression and elevated hepatic AMPK phosphorylation (Alam et al., 2014; Jia et al., 2015).

Naringin and naringenin regulated AMPK activation and increase glucose uptake, improved glucose intolerance and insulin sensitivity (Alam et al., 2014). Bavachin from fruit of *Psoralea corylifolia* was noted for antihyperglycemic effect via increasing plasma insulin and decrease blood glucose and TCH levels in T2DM rats (Lee et al., 2016). It was also reported as non-competitive inhibitor of Acyl-coenzyme A: cholesterol acyltransferase (ACAT) in HepG2 cells, an enzyme that catalyzes cholesterol esterification, important in cholesterol absorption from intestine (Cheng et al., 2010). Pinobanksin isolated and characterized from several plants was reported to be a potent neuroprotective due to its antioxidative potential lowering the intra and inter cellular levels of AGEs (Hong et al., 2012; Boisard et al., 2014). Dihydro myricetin, another flavnone activates insulin signaling and glucose uptake in skeletal muscles and up-regulates degradation of sequestosome 1 and autophagosomes formation by activating AMPK-PGC-1α-Sirt3 signaling pathway that further increases GLUT-4 translocation (Shi et al., 2015; Liu et al., 2018). Diosmin of *Scrophularia nodosa* isolated from the pericarp of citrus fruits regulates HbA1c levels and increased GPx, SOD, and CAT activities (Srinivasan and Pari 2012). The flavanone, eriodictyol proved its antioxidative potential and showed increased mRNA expression of PPAR-γ2 and adipocyte specific fatty acid binding protein (Zhang et al., 2012). Liquiritigenin and isoliquiritigenin, the flavonoidal molecules showed to regulated the glucose uptake process (Dabur, 2017).

Anthocyanins are flavanols that contain a center ring with double bond between C2 and C3 with protonated oxygen making a specific category. These molecules provide different colours in fruits and flowers and received considerable focus as natural colouring agents having antioxidative potential. The anthocyanins like pelargonidin, delphinidin, malvidin, peonidin and petunidin were proven for their therapeutic values. Others in the class were cyanidin, apigeninidin, aurantinidin, 6- hydroxycyanidin, leuteolinidin, tracetidin, and hirustidin. Pelargonidin of berries were validated against hyperglycemia, oxidative stress, glycation via inhibiting phosphorylation of MAPKs, pro-inflammatory cytokines, cecal ligation and endothelial cell protein C receptor shedding (Noda et al., 2002; Jayaprakasam et al., 2005). Cyanidin-3-galactoside was proved to inhibit intestinal α-glucosidase and pancreatic α-amylase (Tsuda et al., 2005; Akkarachiyasit et al., 2010; Matsukawa et al., 2016; Sohanaki et al., 2016; Ho et al., 2017; Matsukawa et al., 2017). Delphinidin and its derivatives were documented for antioxidant activity by decreasing the glycation rate and G-6Pase activity (Tsuda et al., 2005). Delphinidin chloride was reported to prevent endothelial cell function injury associated with T2DM and oxidative stress through regulating microvascular permeability and leukocytes adhering to the venular vessels (Kato et al., 2015; Daveri et al., 2018). Malvidin and cyanidin from *Daucus carota* were reported to increase the expression of CPT-1, PPAR-α and decrease the expression of FAS and SREBP-1c which in turn reduced hepatic

triglyceride levels (Bharat et al., 2018; Kalita et al., 2018). Anthocyanin from *Aronia melanocarpa* regulates glucose and lipid metabolism hence, improved the hepatic steatosis and liver injury reversed due to obesity. It was also found to decrease IL-6 and TNF-α level and increase the IR, p-IRS and p-AKT levels (Takikawa et al., 2010). Shamimin of *Bombax ceiba* showed potentiality against hyperglycaemia in rats. Kakonein from root of *Pueraria lobata* lowers blood glucose level of alloxan or adrenalin induced diabetic mice (Saleem et al., 1999).

Phenolics

Non-flavanoid phenolics contain hydroxycinnamic (C6C3) and hydroxybenzoic (C6C1) constitutive carbon frameworks categorized into phenolic acids, quinines, stilbenes, and coumarins known for antimicrobial activities, nutritional values and also for their anti-diabetic efficacy in different T2DM models by reducing IL-1β, IL-8, MCP-1, and COX-2 or iNOS synthesis. Some phenolics prevent secondary complication of T2DM, such as retinopathy, cardiopathy and nephropathy.

Phenolic acids comprise the derivatives of benzoic acid, hydroxybenzoic acid, cinnamic acid, gallic acid, ellagic acids, caffeic acid, ferulic acid and p-coumaric acids. 4-Hydroxybenzoic acid was found to decrease the plasma glucose levels without affecting serum insulin and liver glycogen contents.

Hydroxycinnamic acid derivatives like cinnamic acid, p-coumaric acid, caffeic, ferulic acid, chlorogenic acid and rosmarinic acid were proved as potent antioxidant and anti-inflammation agents by inhibiting macrophage infiltration, NF- κB activation, reduced the expression of TNFα, MCP-1 and plasminogen activator inhibitor type-1 (PAI-1). Further, they prevented adipocyte differentiation and lowered the lipid profile in animals. So, they are useful against diabetes, hyperlipidemia and obesity disorders (Alam et al., 2016).

Active compound anacardic acid, reported as COX inhibitor was isolated from *Anacardium occidentale*. It activates AMPK that increases GLUT translocation to cell membrane and increase glucose transport into C2C12 myo tubes in a concentration-dependent manner (Tedong et al., 2010). Cinnamic acid also normalizes the lipase and angiotensin-converting enzyme (ACE) in high fat diet fed rats and increased the diameter of aorta and aortic arch and avoiding vasoconstriction. Cinnamic acid derivatives like hydroxycinnamic acid were also reported to inhibit PTP1B, a major negative regulator of insulin signaling pathway (Alam et al., 2016). Gallic acid in μM level was reported to increase the expression and secretion of adiponectin by increasing the adipocyte differentiation. It increased the expression of PPAR-γ target proteins and fatty acid binding protein-4 (Nayeem et al., 2016). Caffeate was noted to regulate Nrf2 expression, the nuclear translocation of NF-κB and the downstream expression of endothelial adhesion molecule 1 and restored antioxidant levels by over expressing Nrf2/EpRE pathway in human endothelial cells (Oboh et al., 2015).

Ferulate also up-regulates the expression of Nrf2 and inhibits the expression of TNF-α and IL-1β by inhibiting the activation of NF-κB and prevents the cell apoptosis and decreases the oxidative stress (Mancuso and Santangelo 2014; Ghosh et al., 2017).

p-Coumarate was found to inhibit adipogenesis, GPDH activity and the expression of PPARγ, C/EBPα and leptin and up-regulated the expression of adiponectin in 3T3-L1 adipocytes and decreased the cholesterol and triglyceride levels in plasma (Alam et al., 2016; Pei et al., 2016). Chlorogenate showed negative relation with fasting blood glucose, glycated hemoglobin and C-reactive protein (Mallavadhani and Sahu, 2003; Dabur, 2017). Masoprocol isolated from *Larrea tridentata* reduced plasma glucose in male C57BL/ks-db/db or C57BL/6Job/ob mice models of T2DM (Luo et al., 1998). It is a potent inhibitor of lipoxygenase, formyl tetra hydrofolate synthetase, carboxylesterase, and cyclooxygenase activities (Luo et al., 1998). Quinones are synthesized via metabolism of hydroquinones or catechols. These are highly reactive and as result generate superoxide anion radicals as antimicrobials (Ahn et al., 2007; Gandhi et al., 2018).

Stilbenes are secondary plant metabolites having two aromatic rings linked by an ethane bridge. Resveratrol, pterostilbene, piceatannol, lonchocarpene and 3, 5- dimethoxy-4′-*O*-prenyl-*trans*-stilbene are examples of this group (Pereira et al., 2012; Kawakami et al., 2014; Yang et al., 2015).

Coumarins are benzopyrones with range of substitutional modifications. They are reported as antibacterial, anti-inflammatory, anti-thrombotic, hepato-protective, antiviral, anti-carcinogenic, and vasodilator agents. Warfarin, 4-hydroxycoumarin, coumarin, psoralen, asinensins, 4-methylumbelliferone, angelicin, osthole, acenocoumarol, dicumarol, citropten, methoxsalen are examples.

The compound is capable of regulating plasma glucose and lipid peroxides and increases the plasma insulin and antioxidant enzymes significantly in the STZ-nicotinamide (NA)-induced T2DM rats (Leach and Kumar, 2012; Medagama, 2015).

Cinnamaldehyde induces glucose uptake and insulin sensitivity in skeletal muscles and adipose tissues in diabetic animals (Zhu et al., 2017). Umbelliferone was reported by Ali et al., (2016) to normalize the levels of glucose, sialic acid, total hexoses, fucose, and hexosamines in STZ-diabetic rats, thereby reducing the glycoprotein formation. It also decreased the levels of blood glucose and lipid peroxidation markers and nonenzymatic antioxidants.

Skimmin from *Hydrangea paniculata*, was reported to decrease the serum creatinine and glucose levels and increase the creatinine clearance significantly in the same way as standard drug losartan-treated rats (Zhang et al., 2012). Coumarins from *Urtica dentata* were reported to be reno-protective in T2DM nephropathy and also found to inhibit high glucose-induced HBZY-1 cell proliferation and hypertrophy mediated through TGF-β1, connective tissue growth factor, and TLR 4 modulation (Cao et al., 2015).

Xanthones like mangostins, swerchirin, mangiferin, norathyriol and cudratricusxanthone are polyphenols close to flavonoids with two benzene rings attached with carbonyl group and oxygen that restrict the free rotation about the carbon-carbon bonds. They are reported to have antidiabetic properties. Other natural xanthones are α-mangostin and γ- mangostin, 3,5,6,8- tetrahydroxyxanthone-1-C-β-D-glucoside, 7-hydroxy-3,4,8- trimethoxyxanthone-1-O-(β-D-glucoside), 6-hydroxy-3,5- dimethoxyxanthone-1-O-(β-D-glucoside) and 3,4,7,8- tetramethoxyxanthone-1-O-(β-D-glucoside). Mangiferin of *Mangifera indica* has been reported for anti-diabetic as well as antihyperlipidemic properties. It was reported to decrease blood glucose level in KKAy mice model of T2DM by increasing insulin sensitivity (Matkowski et al., 2013; Wang et al., 2014). Cudratricusxanthone A, an isoprenylated xanthone prevents NF-κB and JAK/STAT activation, cytokine induced NO production, iNOS expression, inhibited glucose-stimulated insulin secretion and prevented functional β- cell damage. 1, 3, 7-trihydroxyxanthone and 1, 3-dihydroxybenzoxanthone were reported to be non-competitive inhibitors of α- glucosidase through inducing a loss in the α-helix content of α- glucosidase.

Triterpenes

Triterpenes are synthesized through squalene epoxide arrangement followed by condensation involved in defense. They have structural similarity with steroidal hormones, therefore, their mechanism of action is speculated to regulate gene expression under control of glucocorticoid responsive elements (GRE). Binding with GRE suppresses pro-inflammatory and enhance anti-inflammatory protein expression (Liu et al., 2013). They are grouped into pentacyclic, tetracyclic and acyclic triterpenes.

Pentacyclic triterpenes are most abundant triterpenes in flowering plants grouped into oleananes, ursane, lupane, hopane, gammacerane, oleanolic and urosolic acids (oleananes and ursanes).

Oleanolic acid was binds with GRE or muscarinic M3 receptors in pancreatic β-cells linked to anti-inflammatory action and increases archidonic acid secretion. Oleanane-type triterpene bartogenic acid from seeds of *Barringtonia racemosa* displayed α-amylase and α-glucosidase inhibitory activities (Benalla et al., 2010). Glycyrrhizic acid was reported to increase AMPK, SIRT1 and Mn- SOD expression in high glucose treated NRK-52E cells, therefore, it may be useful to treat T2DM and oxidative stress (Li et al., 2014). β-amyrin palmitate from *Protium heptaphyllum* had remarkable antihyperglycemic activity at a very low dose probably by blocking the entry of glucose from the intestine (Santos et al., 2012). The mixture of ursolic and oleanolic acids from *Phyllanthus amarus* was found to have porcine pancreatic α-amylase inhibition. Similarly, *Melaleuca leucadendron* ursolic acid inhibits PTP1B, α-glucosidase and formed new blood vessels in retinal tissue by decreasing the expressions of VEGF, COX-2 and MMP-2 (Liu, 2005).

Purified corosolic acid from the leaves of *Lagerstromea speciosa* (Lythraceae) was an inhibitor of α-glucosidase as compared to acarbose. Euscaphic and p-coumaroylursolic acids of *Sanguisorba tenuifolia* exhibits α-glucosidase inhibitory activity comparable with acarbose. Maslinic acid inhibits glycogen phosphorylase and therefore, increases glycogen content in HepG2 cells (Li et al., 2014; Ladurner et al., 2017).

Betulin (Lupanes) the triterpene isolated initially from birch bark and later from several species of Betulaceae was capable of decreasing blood glucose level and inhibit α-glucosidase and SREBP activity when compared with acarbose (Tang et al., 2011).

Lupeol was also reported to deplete fasting glucose levels and reverse the serum/urine protein, urea, creatinine, polyphagia, polydipsia, and polyuria in alloxan induced T2DM rats by reducing the HbA1c extent and increased the insulin and Hb levels. It was seen to modulate AST, ALT, ALP; HK; G-6-PDase; G-6-Pase, F-1,6-BPase, LDH and pyruvate kinase activities in T2DM rats. Thus, it increases the hepatic glucose utilization in T2DM rats by stimulating insulin secretion from β-cells along with antioxidant activities (Siddique and Saleem 2011). Hopane and lupine are steroidal terpeniods. 29-Nor-21α- H-hopane-3, 22-dione, 21α-H-hop-22(29)-ene-3β, 30-diol and botulin from *Salacia chinensis* stems were reported to inhibit α-glucosidase and aldose reductase. They also showed antioxidative potential (Tran et al., 2008). Ganosporeric acid A decreased GPT activity after CCl_4 and GaIN induced liver injury (Xia et al., 2014). Gammacerane less explored like tetrahymanol, epihakonanediol, ketohakonanol and hakonanediol were isolated from *Adiantum monochlamys* (Shiojima and Ageta, 1994). Tetracyclic triterpenes are less common in nature as compared to pentacyclic triterpenes with four ring structures and similar to sterols, except for the three methyl group substituents at the C-4, and C-14 positions. They are tetracyclic derivatives of dammarane, cucurbitane, euphane, protostane, lanostane, and cycloartane.

Dammarane derivatives are reported from Araliaceae, Cucurbitaceae, Scrophulariaceae, and Rhamnaceae. *Gynostemma pentaphyllum* showed three compounds namely, 20S)-dammarane-24(25)-ene- 3b,20,21-tetrol, (20R,23R)-3b,20-dihydroxyldammarane-24- ene-21-oic acid-21,23-lactone and 3b-hydroxyetio-17bdammaranic acid which inhibited PTB1B. Cucurbitacin from *Momordica charantia* have been reported to have permeability problem and hence, are less absorbed through the intestine (Tan et al., 2008). Eupahne triterpenes such as euphane-3β, 20-dihydroxy-24-ene was identified from roots of *Euphorbia kansui* and reported to be an inhibitor of oxidoreductase 11β-hydroxysteroids dehydrogenase type 1 (11β-HSD1). 11β-HSD1 catalyses conversion of cortisone to active cortisol and cortcosterone, required for body growth and maintenance that have role in type 2 diabetes. Hence, inhibitors of 11β-HSD1 offer a potential therapy to manage T2DM (Guo et al., 2012). Bark extracts of *Boswellia serrata* containing 20, 24 dihydroxyeupha-2, 8, 22-triene showed anti-inflammatory activities (Singh and Bhakuni, 2006). Protostanes are the stereoisomer of dammarane type triterpenes, with structural rearrangement in 8α-CH3, 9β-H, 13α-H, and 14β-CH3 positions found in Alismataceae. Alisol A, alisol B, alisol A 24- acetate and alisol B 23-acetate identified from *Alismatis rhizoma* were found to be effectively delaying cholesterolemic effects (Lin, 2014). Lanostanes are less frequent and was characterized by the *trans* ring junction of the A/B, B/C, and C/D rings and reported from sponges and fungi. They were reported for their antiproliferative activity. However, Ganoderic acid A, Ganoderic acid H and lucidenic acid B from *Ganoderma lucidum* were reported for their anti-inflammatory and antiageing activity through inhibition of NF-KB in mice. Further, they improve the insulin sensitivity through regulation of SREPB pathway (Zhu et al., 2018). Butyl ganoderate A, butyl ganoderate B, butyl lucidenate N, and butyl lucidenate A were reported for inhibitory effects on adipogenesis in 3T3-L1 cells through down-regulation of SREBP-1c (Lee et al., 2010). *Poria cocos*, known as Bai Fu Ling in Chinese was reported to contain lanostane-type triterpene, dehydrotrametenolic acid and dehydrotumulosic acid, found to be effective in hyperglycemia (Wang et al., 2015). Cycloartanes or 9, 19-cyclolanostanes of *Astragalus membranaceus, Passiflora edulis* and *Cimicifuga racemosa* was reported to increase the glucose uptake and decrease the lipid accumulation in 3T3- L1 adipocytes through increasing the expression levels of PPARγ and GLUT4 expression. *Lagerstroemia speciosa* leaves showed significant glucose transport-stimulating activity and significantly reduced blood glucose levels (Judy et al., 2003). Azadiradione and gedunin, limonoids from *Azadirachta indica* reduced postprandial hyperglycemia by inhibiting HPA (anti-diabetic target) (Ponnusamy et al., 2015). Abietane-type diterpenoids, danshenols A and B isolated from roots and rhizome of *Salvia miltiorrhiza* showed inhibitory activity against rat lens. Tinosporaside isolated from ethanolic extract of *Tinospora cordifolia* tends to have antihyperglycemic activity in STZ model as compared to metformin (Maurya et al., 1995). Limonoids from *Swietenia humilis*, 2-hydroxy-destigloyl-6-deoxyswietenine acetate, humulin B, methyl-2-hydroxy-3-β-tigloyloxy-1- oxomeliac-8(30)-enate were found to decrease the glycemia and increase hepatic glycogen contents in STZ-induced T2DM rats. Catalpol isolated from *Rehmannia glutinosa* roots has been reported to act on AMPK/NOX4/PI3K/AKT pathway thereby exhibiting anti-diabetic effects *in vivo* and *in vitro* (Yan et al., 2018).

Phytomolecules like terpenoids, alkaloids, flavonoids, phenolics, and some other categories have shown antidiabetic potential through the insulin mimetic activity of the plant extract.

Roseoside, epigallocatechin gallate, beta-pyrazol-1-ylalanine, cinchonain Ib, leucocyandin 3-O-beta-d-galactosyl cellobioside, leucopelargonidin-3-O-alpha-L rhamnoside, glycyrrhetinic acid, dehydrotrametenolic acid, strictinin, isostrictinin and pedunculagin, epicatechin and christinin-A isolated from plants have shown significant insulin mimetic activity along with significant antidiabetic potential. Additionally, some flavonoids and polyphenols, as well as sugar derivatives, are found to be effective due to some other extra pancreatic mechanisms. Jung et al. (2006) recorded a number of plants which have shown antidiabetic action through release of insulin and some extra pancreatic mechanisms. Modak et al., (2007) and Jarald et al. (2008) documented *Allium cepa*, *Clerodendron phlomoides*, *Cinnamomum tamala*, *Coccinia indica*, *Enicostemma littorale*, *Ficus benghalensis*, *Gymnema sylvestre*, *Momordica charantia*, *Pterocarpus marsupium* and *Syzygium cumini* to have a great antidiabetic potential, which have already been subjected to the clinical trials. Some marketed herbal formulations (diasulin, pancreatic tonic 180 cp, chakrapani, diabecon, bitter gourd powder, dia-car, diabetes-daily care, gurmar powder, epinsulin, diabecure, syndrex, diabetawhich) which have been proved for the antidiabetic activity are also listed in the database. Although all these plants have shown varying degrees of hypoglycemic and anti-hyperglycemic activity not all were effective in severe experimental diabetes and its related complications (Grover et al., 2002). A novel anti-hyperglycemic amino acid has been extracted and purified from fenugreek seeds (4-hydroxyleucine) which reportedly increases glucose-induced insulin release. Mousavi et al. (2020) proved antidiabetic and *in vitro* enzyme inhibition studies of methanol extract of *Ocimum tenuiflorum* leaves and its fractions. Patel et al. (2012) reviewed antidiabetic medicinal plants having insulin mimetic property. Sachithanandam et al. (2019) also analyzed antidiabetic properties of Indian mangrove plants.

Conclusion

Many plant species contain polyphenols that contain more than two phenolic hydroxyl groups and are natural antioxidants and can provide health benefits to humans. These polyphenols include, for example, oleuropein, hydroxytyrosol, catechin, chlorogenic acids, hesperidin, nobiletin, and isoflavones. Based on the ingredient functionality of phenolic compounds in various food systems and their safer and efficacious dose for humans, it is possible to develop nutraceuticals or functional foods for type 2 diabetic patients. Preserving the native structure of the active molecules during functional food preparation is important. Keeping a balance between α-amylase and α-glucosidase inhibitors would be useful to limit the gastrointestinal adverse effects related to undigested starch reaching the colon. For the development of nutraceuticals or functional foods, knowledge of the interaction between phenolic compounds and digestive enzymes is desirable

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