Mechanistic approach of anti-diabetic compounds identified from natural sources

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ABSTRACT

Type-2 diabetes mellitus (T2DM) is a global disease, which leads to various other life threatening diseases and affects the quality of life. Current therapies of T2DM have various side effects and ultimately lead to insulin resistance, along with financial burden. Therefore, comparative study of natural compounds along with their mechanisms has been discussed, which may lead toward the better understanding about their efficacy and selection of future anti-diabetic drugs. Traditional medicine is promising to treat T2DM, where more than 200 plants and other species are shown to have anti-T2DM effects. Moreover, these natural products have different types of molecular mechanisms, i.e. β-cell regeneration, insulin mimicry, AMPK, Akt, PPARs, LXR activation and inhibition of α-glucosidase, TNF-α, sodium glucose co-transporters and oxidative stress. At the same time a number of compounds have been reported to have in vivo efficacy. As a number of investigators speculated the molecular mechanism of these natural compounds, hence this review is focused on the molecular mechanism of different types of natural anti-diabetic molecules and their classes along with their efficacy in animal models. This review will provide a broad idea about anti-diabetic compounds to scientific and common people and will help to choose the dietary components and traditional medicines effective in T2DM.

Keywords: Diabetes mellitus, natural products, mechanism of action, alkaloids, flavonoids, triterpenes, glycosides, saponins

INTRODUCTION

Type-2 diabetes mellitus (T2DM) is the metabolic disorder of the endocrine system, presently affecting about 5-10% of the population of the World. By the year 2030, it will affect 366 million people as estimated by World Health Organization (WHO) and therefore, declared epidemic.1 Diabetes is characterized by abnormal high blood glucose levels resulting in defects in insulin secretion or action further causing alteration in carbohydrate, protein and lipid metabolism. T2DM is usually found in adults and associated with insufficient production of insulin or loss of responsiveness of cells to insulin.

Glucose production by hepatocytes and its consumption by extrahepatic cells are fine-tuned biological processes to maintain the proper physiological state of body. Glucose homeostasis is regulated by a number of factors and processes that include glucose transporters, hormones, neuronal signals, and physiological status of body. Any alteration in these factors, leads to alteration in glucose homeostasis and adverse conditions i.e. diabetes, obesity, hyperlipidemia, cardiac, renal and others disorders.2 In glucose homeostasis disorders, T2DM is characterized by comparative insulin deficiency and insulin resistance that accounts for more than 90% of the total diabetes cases around the globe.3 T2DM adversely affects the human physiology and leads to more complicated situations such as liver and brain damage, renal and cardiac problems, skeletal muscle loss, kidney failure and eye diseases. European Research Council and the America Diabetes Association’s Standards of Medical Care in diabetes have described T2DM as chronic illness without cure.

Glucose metabolism is inter-linked with fatty acid, amino acid metabolism, gluconeogenesis, and glycogenesis. In normal physiological conditions, pancreatic β-cell secretes insulin in response to increase in blood glucose directed by a hormonal cascade initiated from hypothalamus. Insulin binds with insulin receptors and increases the translocation of glucose transporter subtype 4 (GLUT4) and therefore glucose uptake inside the cells. It increases the ATP/ADP ratios that inhibits ATP sensitive K+ channels and generate voltage dependent Ca++ influx. Elevation of Ca++ triggers the exocytotic release of...
insulin. This is the main cycle to control blood glucose levels. Additionally, several hormones, neurotransmitters, peptide hormones (glucagon peptide-1) increases the cAMP levels, which also potentiates the effects of insulin. Insulin also increases the Akt/PKB expression that up-regulates the activity of glycogen synthase, glucosidase and inhibits GSK-3. It stimulates the glycogenesis, glycolysis and gluconeogenesis pathways. Insulin secretion is negatively correlated to glucagon secretion and therefore reduces glucose production from glycogen, release of fatty acids and glycerol from adipocytes. Moreover, insulin promotes the de novo lipogenesis and reduces production of ketone bodies, a major problem in T2DM. During physiological stress conditions i.e. exercise, glucose uptake in skeletal muscle cells increase additionally via AMP-activated protein kinase (AMPK), independent from insulin dependent pathway. All the biological processes discussed above get reversed in T2DM condition, when cells lose insulin sensitivity or decreased insulin production. Decreased insulin sensitivity or insulin resistance decrease the glucose uptake in cells, which triggers the cell to explore alternate energy sources and increase lipolysis, hepatic glucose production. Overall, decreased glucose uptake, β-cell dysfunction, gluconeogenesis, lipolysis, ketogenesis are the main characteristic features of T2DM.

A number of pharmacological and non-pharmacological majors have to be taken to regulate hyperglycemia in T2DM patients. A number of compounds/natural products have been reported as analogues of synthetic anti-diabetic drugs i.e. insulin sensitizer, insulin scetrogogues, sodium-glucose co-transporter 2 inhibitors, bile acid sequestrants, dipeptidyl peptidase-4 inhibitors, glucagon like peptide-1 receptor agonists/analogues and α-glucosidase inhibitor. However, in majority cases mechanism of actions of these compounds has not been established therefore, these are unfit for clinical trials. Although, the in vivo efficacy of these compounds can be established through clinical trials, it would be possible to establish a network between anti-diabetic drugs and their detailed action mechanism in T2DM pathology in systemic manner. Thus, the goal of present article is to discuss the detailed mechanistic information along with molecular targets of anti-diabetic natural products including alkaloids, phenols, terpenoids, flavonoids, saponins, xanthones, polysaccharides and other anti-diabetic compounds.

**ALKALOIDS**

Alkaloids are nitrogen containing heterocyclic compounds having different types of ring structure. On the basis of ring structure, these can be classified into 14 sub classes. As structure of these compounds varies, they also have different molecular targets and therefore, mechanisms of action. Most of the alkaloids are cytotoxic at higher concentrations; therefore, they have anti-cancerous properties and cannot be used to treat T2DM. In majority, only four classes of alkaloids, namely indole, isoquinoline, amino and terpenoidal alkaloids have been reported for anti-diabetic activities.

**Isoquinoline alkaloids:** Isoquinoline alkaloids have been reported for a wide range of biological activities. Morphine and codeine are the typical examples of this category. These are well known opioid analgesics and are used to relieve pain. Most of alkaloids in this category are reported to binds with opioid, serotonin and dopamine receptors and affect the central nervous system due to similar active nitrogen molecule to neurotransmitters that influence their binding to the receptors. Recently, it has been reported from several laboratories that dopamine receptors agonist ameliorate hyperglycemic condition and elevate basal insulin release. Boldine, palmatine, jatrorrhizine, and berberine are the isoquinoline alkaloids reported to have anti-diabetic activities.

In this category berberine (PubChem CID: 2353) is the most studied alkaloid. It was isolated from various plants including Berberis vulgaris L., B. aquifolium (Berberidaceae), Coptis chinensis Franch. (Ranunculaceae), Hydrastis canadensis, Poir. (Ranunculaceae) and Tinospora cordifolia (Wild) Miers (Menispermacae) and has potent hypoglycemic activity. Berberine improves the action of insulin by activating an enzyme, AMP-activated protein kinase i.e. AMPK which helps in regulating the cellular uptake of glucose, the oxidation of fatty acids and the synthesis of glucose transporter 4 (GLUT4), the insulin-regulated glucose carrier found in skeletal and cardiac muscle that is responsible for moving glucose from the bloodstream to cells. It also increases the expression of insulin receptors. The increase in number and activity enables the same amount of insulin to be more effective. Another way of describing this activity of berberine is decreasing insulin resistance. Other researchers have reported that berberine inhibits an enzyme protein tyrosine phosphatase 1B (PTP1B), which in turn inhibits the insulin receptors. Berberine was reported to regulate blood sugar by increasing the secretion of one of the major incretins, glucagon-like peptide 1 (GLP-1). Yet, another aspect of the blood sugar regulating action of berberine is its ability to inhibit dipeptidyl peptidase 4 (DPP-IV). When DDP-IV is inhibited, GLP-1 and other gut-secreted incretins are not broken down as rapidly, so they can continue to stimulate insulin and inhibit glucagon release significantly (Figure 1).

Boldine (PubChem CID: 10154) initially isolated from Peumus boldus Molina (Monimiaceae) was reported to reduce the glucose levels and oxidative stress in STZ-induced diabetic rats. It has been reported to decompose reactive oxygen species and stabilize NO production by increasing eNOS phosphorylation that increases NO bioavailability in the STZ-induced diabetic rats. It was also reported to prevent the increase in hemi channel activity and a loss of cell communication via gap junctions in mesangial cells supported by an increase in Cx43 protein levels. Palmatine (PubChem CID: 19009) was also reported to be effective to control hyperlipidemic and hyperglycemic conditions. It was reported to activate or increase the expression of PPARα. It is also reported to induce expression of GLUT-4 by 5-fold. Jatrorrhizine (PubChem CID: 72323), a compound in same category also reported to reduce the blood glucose in normal
and hyperglycemic mice. Moreover, it was found to inhibit the platelet aggregation in rabbits. One recently published study from our lab demonstrated that jatrorrhizine and palmatine are competitive agonists of DDRs and also inhibit dopamine catabolism that increases the dopamine levels. Both factors lead to DDRs activation and increased cAMP synthesis that mediate protein kinase A activation, therefore, phosphorylation of proteins including PPARα. Phosphorylation of PPARα enhances its binding to PPRE and activates the transcription of multiple genes involved in lipid metabolism and GLUT4. One common feature present in the isoquinoline alkaloids was their affinity toward opioid and dopamine receptors.

Trigonelline (PubChem CID: 5570) is potential active principle and major alkaloid of Trigonella foenum-graecum (Fabaceae) also known as fenugreek. It is reported to have hypoglycemic activity. Moreover, it reduces diabetic auditory neuropathy, affects β cell regeneration, insulin secretion, and activities of glucose metabolism related enzymes. Trigonelline increase the glucokinase/glucose-6-phosphatase (G6Pase) ratio in the liver and decrease the TNF-α level in serum in the diabetic mice. It is also reported to decrease the activity of liver fatty acid synthase, and increase the activity of liver carnitine palmityl transferase and glucokinase. Due to the control of these events trigonelline significantly improves glucose and lipid homeostasis by increasing GLUT4 expression and translocation, inhibiting FFAs, and oxidative stress. It brings its hypoglycemic effect by increasing the levels of serum insulin, increasing the sensitivity of tissues to insulin action and by stimulating the activity of enzymes of glucose utilization. Trigonelline was reported to increase insulin sensitization through moderating ER stress by decreasing ER stress protein expression, decreasing the oxidative stress, TNF-α levels and activation of PPARγ in adipose tissue (Figure 1).

**Indole alkaloids**: A number of indole alkaloids from various plant sources have been reported for their anti-diabetic potential, namely harmine (PubChem CID: 5280953), vindoline (PubChem CID: 260535), vindolindine, vindolicine, vindolinine, koenidine, canthin-6-one (PubChem CID: 97176), mahanimbine (PubChem CID: 167963), and catharanthine (PubChem CID: 72315). Mahanimbine, koenidine and carbazole (PubChem CID: 6854) alkaloids isolated from leaves of Murraya koenigii Linn., (Rutaceae) were reported to effect the elevated blood glucose, serum lipids in STZ-induced diabetic rats and inhibit α-amylase and α-glucosidase. The possible mechanism by which the mycaminose and mahanimbine decreases blood sugar level may be by potentiating of insulin effect, either by increasing the pancreatic secretion of insulin from beta cells of islets of langerhans or by increasing the peripheral glucose uptake. Its mechanism is unknown, as compounds are reported to bind with microtubule-associated protein tau. It is not a well studied compound and therefore, targets of compound have not been identified. Koenidine is reported as metabolically stable compound that reduced postprandial blood glucose levels and improved insulin sensitivity.

![Figure 1: Schematic representation of proposed mechanism of action of alkaloids in prevention of type-II diabetes mellitus. Green and red arrows indicate the increased and decreased activity of enzyme(s).](image-url)
sensitivity. Koendine increased the AKT-dependent signaling pathway mediated GLUT4 translocation in L6-GLUT4 myc myotubes (Figure 1).  

Harmine was isolated and characterized as major alkaloid from Peganum harmala L. (Zygophyllaceae). It is a competitive inhibitor of tyrosine-regulated kinase-1a (Dyrk1A) and promotes β cell proliferation and differentiation. It was also reported to inhibit monoamine oxidases, and cdc-like kinases. Dyrk1A phosphorylate glycogen synthase kinase 3β (GSK3β) to inhibit its activity. GSK3β phosphorylate glycogen synthase-3 (GS-3) and phosphorylation of insulin receptor (IRS1) and regulate their activities. Selective inhibition of GS-3 improves the insulin-stimulated glucose transport because of increased GLUT-4 glucose transporter translocation and post-insulin receptor insulin signaling. Moreover, overexpression of Dyrk1A has been reported to suppress the PPAR-γ expression. Inhibition of GS-3 diverts glucose to glycolysis. Therefore, it is directly involved in glucose homeostasis. Despite of this, harmine is well known for hallucinogenic properties and cannot be used to treat T2DM conditions. However, synthetic harmine analogues may be the good source of Dyrk1A inhibitors (Figure 1).  

Indole alkaloids from Catharanthus roseus Linn. (Apocynaceae) namely, vindoline, vindolidine, and vindolicine were reported to be non-cytotoxic upto 25.0 µg/mL towards pancreatic β-TC6 cells and induce glucose uptake in pancreatic β-TC6 as well as in C2C12 cells (Table 1). These compounds were reported to inhibit protein tyrosine phosphatase-1B (PTP-1B) activity (Figure 1). PTP1B acts as a negative regulator of insulin and leptin signal transduction, and this implies its therapeutic potential in T2DM. Overexpression of PTP1B is reported to impair the activity of insulin receptors and PI3 kinase that decrease the muscle glucose uptake. In contrast inhibition of PTP1B increases the GSK-3β and PKB phosphorylation thereby increasing insulin sensitivity and works in the same way as in case of harmine. Studies support the fact that genetically silenced PTP1B animals have increased insulin dependent metabolic signaling and improves the insulin sensitivity. In addition, vindoline also showed good antioxidant potential. Another alkaloid from C. roseus, catharanthine has also been reported to lower blood sugar levels. Catharanthine stimulates release of amylase and induces a delayed release of Ca2+ from pancreas. It was reported to significantly increase the hexokinase activity and decrease the glucose 6-phosphatase and fructose 1, 6- bisphosphatase activities. Therefore, it increases glycolysis.  

Piperidine alkaloids: Tecomine (PubChem CID: 442553) isolated from Tecoma stans Linn. (Bignoniaceae) is reported to significantly increase of glucose uptake rate in rat adipocytes from normoglycemic rats. It has also been found to exert a potent stimulating effect on basal glucose uptake with an IC50 value 6.79 x 10−9 M. The anti-diabetic activity of ethanolic extract of T. stans stem may be due to potentiation of insulin secretion from β-cells of pancreas, i.e. pancreatotropic action. Piperidine flavan alkaloids were isolated from Combretum micranthum (Combretaceae), commonly known as kinkeliba. These alkaloids showed anti-diabetic properties and found to decrease the phosphoenolpyruvate carboxykinase (PEPCK) gene expression, related to hepatic glucose production. Piper retrofractum (Piperaceae) fruits contain piperine (PubChem CID: 638024), pipernaline (PubChem CID: 9974595), and dehydropipernaline (PubChem CID: 6439947). These alkaloids are reported to activate AMPK signaling and the PPAR-γ that make these potential antidiabetic agents (Figure 1). Food-grade phenolics from dietary plant extracts inhibiting α-amylase activity are potentially safer, and therefore may be a preferred alternative for modulation of carbohydrate digestion and control of glycemic index of food products. Semi purified fraction from water extract seeds of fenugreek (Trigonella foenum-graecum Linn.) was reported to have antihyperglycemic efficacy at dose of 50 mg/kg bw comparable to tolbutamide.  

**Amino alkaloids**: Aegeline (PubChem CID: 15558419), an alkaloidal-amide, isolated from leaves of Angle marmelos (Linn.) Corr. Serr; was reported to have antihyperglycemic activity in STZ induced diabetic rats. Alkaloidal fraction from the plant containing aegeline and marmeline was reported to significantly reduce blood glucose to 90.12±5.81 mg/dl as compared to 342.14±14.89 mg/dl in alloxan induced diabetic animal model. It also found to increase liver glycogen in diabetic animals. The hypoglycemic activity of aegeline was due to the enhanced GLUT-4 translocation. It inhibits the activities of Akt and Rac1 that suggests the aegeline stimulated distinct parallel glucose transport. Aegeline also activates p21 protein activated kinase-1 (PAK-1) and coflin, an actin polymerization regulator. It suggests the stimulation of PI3 kinase-Rac1-PAK1-cofilin pathway. Moreover, aegeline is also involved in the intracellular Ca2+ signaling events. Overall, aegeline control the multiple cellular processes to control T2DM (Figure 1).  

**Alkaloid rich extracts**: Alkaloid rich fraction of Capparis decidua (Capparidaceae) contains spermidine alkaloids i.e. cadabicine (PubChem CID: 100921101), isocodonocarpine, codonocarpine (PubChem CID: 5281820), and capparidisine significantly inhibited the elevation of blood glucose level. These compounds were also reported to decrease the total cholesterol and triglyceride levels (p<0.05). Extract was found to inhibit the G6Pase activity by 44%, and increase the liver and muscle glycogen content. It was found to be effective to control T2DM condition by attenuating G6Pase, PECK, aldose reductase and TNF-α expression. At the same time, it increased the expression of GLUT-4, PPAR-γ and glucokinase. The anti-diabetic efficacy of the alkaloids of Acanthus montanus (Acanthaceae) was studied in alloxan-induced diabetic rats. Alkaloids reduced the blood glucose level by 42.68% as compared to glibenclamide. It was also found to significantly (P<0.05) increase the platelet and WBC count and reduce liver enzymes levels, total cholesterol, HDL, triglycerides, and total protein when used for a long period. Morus spp. (Moraceae) latex has been reported to have antidiabetic activities due to very high concentrations of 1,4-dideoxy-1,4-imino-D-arabinitol, 1-deoxynojirimycin (PubChem CID: 29435), and 1,4-dideoxy-1,4-imino-D-ribitol (PubChem CID: 638024, pipernaline (PubChem CID: 9974595), and dehydropipernaline (PubChem CID: 6439947). These alkaloids are reported to activate AMPK signaling and the PPAR-γ that make these potential antidiabetic agents (Figure 1). Food-grade phenolics from dietary plant extracts inhibiting α-amylase activity are potentially safer, and therefore may be a preferred alternative for modulation of carbohydrate digestion and control of glycemic index of food products. Semi purified fraction from water extract seeds of fenugreek (Trigonella foenum-graecum Linn.) was reported to have antihyperglycemic efficacy at dose of 50 mg/kg bw comparable to tolbutamide.  

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CID: 446222), alkaloidal sugar-mimic glycosidase inhibitors.\(^\text{35}\) Alkaloids rich fraction of Aerva lanata Linn. (Amaranthaceae) contains major amounts of alkaloid; canthin-6-one (PubChem CID: 97176) showed significant improvement in streptozotocin-nicotinamide induced T2DM rat model.\(^\text{36}\)

**MECHANISM OF ACTION OF PLANT PHENOLICS**

Phenolics are aromatic compounds having benzene ring with hydroxyl groups. These are produced by plants for their protection against stress. In broad sense, phenolics can be divided into flavanoids and non-flavanoids groups.

**FLAVANOIDS**

These are water soluble polyphenolic molecules containing two benzene rings joined together with a short three carbon chain. Chalcone, flavone, flavonol, flavanone, isoflavonoids and anthocyanins are the major groups in flavonoids. Flavonoids have been reported for anti-inflammatory, antidiabetic, anticancer, neuro-protective and cardio-protective activities. Flavonoids were reported to enhance insulin secretion, promote pancreatic \(\beta\)-cells proliferation, glucose uptake, and reduce insulin resistance, inflammation and oxidative stress.\(^\text{37}\)

**Flavones:** Flavones are benzopyrans and ubiquitously present in fruits and vegetables of daily diet. Examples of flavones are apigenin (PubChem CID: 5280443), luteolin (PubChem CID: 5280445), chrysine (PubChem CID: 57420110), 7-hydroxyflavone (PubChem CID: 5281894), galangin (PubChem CID: 5281614), fisetin (PubChem CID: 5281614), genistein (isoavone) (PubChem CID: 5280961), gardenin (PubChem CID: 261859), tangeretin (PubChem CID: 68077), 8-methoxyflavone (PubChem CID: 213728), hispidulin (PubChem CID: 5281628), and acacetin (PubChem CID: 5280442). Apigenin has been reported to reduce hepatic oxidants, hyperglycemia, hepatic G3Pase and cholesterol in alloxan and STZ induced diabetic rats. Moreover, apigenin was reported to increase AMPK phosphorylation (Figure 2) and therefore, AMPK dependent energy metabolism, helpful in dislipidemic condition.\(^\text{38}\) Luteolin and chrysine were reported to inhibit maltase, improve insulin sensitivity, and Akt phosphorylation through activation of PPAR-\(\gamma\), a central serine thereonine kinase to regulate lipogenesis, glycogenesis, and proliferation. Both compounds were reported deplete NO and ROS levels (Figure 2). Therefore, chrysine and luteolin were claimed to lessen vascular complications associated with insulin resistance through PPAR-\(\gamma\) dependent pathways. However, in another study, luteolin was reported for poor inhibitor of maltase and did not reduce blood glucose level significantly with the doses of 100 and 200 mg/kg. Luteolin was reported to raise adiponectin levels and decrease MCP-1 and resistin levels and increase insulin sensitivity in T2DM mice models. It was also found to increase HO-1 expression, hence attenuate oxidative stress and therefore, diabetic nephropathy. It was reported to decrease MafA, CREB-binding protein/p300, and CBP/p300 protein (NF-\(\kappa\)B coactivator) (Figure 2). Therefore, it ameliorates insulin resistance due to its anti-inflammatory

![Figure 2: Schematic representation of proposed mechanism of flavonoids in management of diabetes mellitus](image-url)
activity and inhibiting NF-κB, iNOS-NO and IKKβ/IRS-1/Akt/eNOS-dependent signaling pathways.39,40

Chrysin was reported to reduce renal TNF-α, transforming growth factor-beta (TGF-β) expression considerably and inhibit the nuclear transcription factor-kappa B (NF-κB) activation (Figure 2). However, no significant differences were observed in fasting blood glucose and serum insulin levels after chrysin treatment. Authors claimed that chrysin inhibits diabetic nephropathy in HFD/STZ-induced type 2 diabetic rats by suppressing TNF-α pathway. Suppression of TNF-α also reduce the serum levels of IL-1β and IL-6.41 In another study, baicalein (PubChem CID: 5281605), a flavonoid from Scutellaria baicalensis Georgi (Lamiaceae) with chrysin, were found to have in vitro anti-α-glucosidase activity. Therefore, chrysin reduce the glucose and lipid peroxidation, improve insulin sensitivity and exerts antidiabetic effects. Moreover, mice treated with baicalein (0.25 or 0.5 g baicalein/kg) in diet were found to have less oxidative burden, HbA1c, AGEs and improved hypoglycemia, glucose tolerance and insulin levels. Baicalein activates AMPK, which phosphorylate IRS-1, AKT and dephosphorylate ERK, JNK and NF-κB that attenuate inflammation and insulin resistance. Activation of AMPK pathway also increases mitochondrial β-oxidation and inhibits fatty acid synthesis and gluconeogenesis. Dephosphorylation (inactivation) of NF-κB decreases the iNOS and TGF-β1 expression that was reported to normalize the renal tissues structural changes (Figure 2). Therefore, AMPK activation decreases the inflammation by reducing TNF-α level and NF-κB activity and oxidative stress and increase the insulin sensitivity. Nishioka et al (1998) reported that 5, 6, 7-κB activity and oxidative stress and increase the insulin decreases the inflammation by reducing TNF -κB. Overall, these molecules evidenced by expression of fatty acid synthase, PPAR-γ and CCAAT/enhancer-binding protein (C/EBP) α. Fisetin was also reported to increase the expression of CPS-I, OTC, ASS and GS and decreased iNOS and NF-κB p65 in hyperammonaemic rats. Therefore, fistein may contribute to control obesity and diabetes. Fistein also inhibit CBP/p300 gene expression and levels of histone acetylation. This suggests the epigenetic changes and therefore, for T2DM fistein was proposed as supplementation (Figure 2).47–49 Further, it is reported to activate antioxidant enzymes and increase glutathione in diabetic rats. It suggests the antioxidative and anti-inflammatory properties of fistein. Further, fistein was reported as a sirtuin activator (anti-ageing) and DNA methyltransferase inhibitor.49–51 The antidiabetic activity of fistein seems to be because of its anti-oxidant activity or anti-oxidant activity boost up its anti-diabetic activity. However, further studies are required to explore its mechanism.

Flavone, tangeretin, found abundantly present in citrus fruits was reported to promote blood body weight, total cholesterol, blood glucose. It was also found to decrease adiponectin, leptin, resistin, and pro-inflammatory cytokines i.e. IL-6, and MCP-1. Tangeretin also modulate glucose homeostasis by increasing glycolytic enzymes and stimulating insulin secretion by secretion of an insulin-resistance factor.52 Wogonin, extracted from the root of Scutellaria baicalensis Gerogi (Scutellariae radix) was also reported to increase insulin sensitivity and decrease blood glucose levels through AMPK activation, as in case of tangeretin. Additionally, it was reported to activate PPARα and inhibit NF-κB. Overall, these molecules attenuate inflammation, decrease ROS and increase insulin sensitivity mediated through AMPK and NF-κB regulated pathways (Figure 2).53,54

Isoflavones: A number of isoflavones i.e. daidzein (PubChem CID: 5281708), genistein, formononetin (PubChem CID: 5280378), biochanin A (PubChem CID: 5280373), cuneatin, luteone, alpinumisoflavone (PubChem CID: 5490139), retusin (PubChem CID: 5352005), tectoridin (PubChem CID: 5281810), and prunetin (PubChem CID: 5281804) have been reported from various plants. Daidzein is a naturally occurring isoflavone found in many plants including Pueraria mirifica and P. lobata (Fabaceae). It has been reported to promote glucose uptake, AMPK phosphorylation and GLUT4 translocation in L6 myotubes (Figure 2), even in the absence of insulin and thereby suppress blood and urinary glucose, and serum cholesterol levels in T2DM models. Moreover, genistein and (S)-equol (produced by gut microflora), are the metabolite of daidzein, reported to induce rat split- and hairy-related protein-2 (SHARP-2) gene expression in H4IIIE rat hepatoma cells. Insulin induced SHARP-2, a transcription factor decreases the expression of the PEPCK gene. (S)-Equol is reported to activate PKC and therefore, PI3K/PKC pathway. It is also reported to activate PKA signaling and inhibit α-glucosidase and suppress the postprandial hyperglycemia. 6,7,4'-Trihydroxyisoflavone, another daidzein related isoflavone has been reported to suppress adipogenesis in 3T3-L1 pre-adipocytes through PI3K (Figure 2).55–59
Genistein, a naturally-occurring soy isoflavone has been reported to increase β-cell proliferation, stimulate insulin secretion, and estrogen receptor. It is also reported for anti-apoptotic, antioxidant potential and inhibits tyrosine kinase. Genistein has been shown to activate calmodulin kinase II (CaMK II) and therefore, Ca^{2+} signaling, important in insulin secretion. It produces proliferating effects on cAMP/PKA and ERK1/2 signaling pathways in β-cells at <10 µM, a physiologically-relevant concentrations that induce the proliferation of INS1 and human islet β-cells. However, results have been contradicted as a previous study has shown the suppressive effects of genistein on ERK1/2. It has been reported to increase insulin-stimulated phosphorylation of insulin receptor-β and insulin receptor substrate-1 (IRS-1) and therefore, phosphatidylinositol-3 kinase (PI3K) and Akt phosphorylation (Figure 2). It also increases the PI3K expression, translocation of GLUT-4 and phosphorylation of AMPK and acetyl coenzyme A carboxylase (ACC) in all the conditions, which reduce the inflammation and improve insulin signaling. However, it has been reported to down-regulate IRS-1, p70 ribosomal protein S6 kinase and S6K1 phosphorylation in the skeletal muscle of high-fructose and high-fat diet (HFFD)-fed mice. It suggests the improved insulin action in the skeletal muscle through AMPK. One study suggested the anti-apoptotic and anti-diabetic effects of genistein were through the GPR30-mediated activation of cAMP signaling. Reports have also indicated the opposite effects of genistein on insulin sensitivity in normal and inflammatory conditions by negative or positive regulation of IRS1. It is reported to impair glucose tolerance and insulin sensitivity in normal conditions by inhibiting IRS1 that inhibit insulin-mediated GLUT4 translocation. Genistein treatment to HFFD-fed animals reported to decrease lipid accumulation by 40%. Therefore, it has been concluded that it down-regulated lipogenesis and upregulated β-oxidation related genes in HFFD-fed mice. In contrast, several previous studies reported only moderate positive effect or neutral effect of dietary isoflavones on plasma lipid profile and T2DM. Moreover, in one study on 253 Chinese women having impaired glucose regulation, genistein and daidzein didn’t produce any significant effect over a six month treatment period. Genistein has also been reported to up-regulate anti-apoptotic protein Bcl-2 expression in β-cells (Figure 2).\textsuperscript{60, 61–67} Pleiotropic effects of isoflavones make them promising candidates to prevent and treat diabetes. However, a greater understanding of the exact mechanisms of genistein may facilitate design of more effective and targeted pharmaceutical compounds with fewer side effects.

Formononetin (PubChem CID: 5280378), an O-methylated isoflavone found in a number of plants and herbs including Astragalus membranaceus (Leguminosae) reported for its cardioprotective, anti-inflammatory, and rejuvenate properties. Formononetin treatment reduced the alloxan-induced fasting blood glucose with Fas and caspase-3 mRNA levels in pancreas tissue. At the same time, it increased the mRNA levels of pancreatic and duodenal homeobox-1, IRS 2, GCK, GLUT 2, and G6Pase along with insulin activity, glycogen level, body weight, and oral glucose tolerance in alloxan-induced T2DM model. In another study, formononetin was reported to prevent IL-1β-induced INS-1 cell death and blocks cytokine-induced apoptotic signaling due to reduction in Bax/Bcl-2 ratio and caspase-3 activity. It was also found to inhibit the NF-κB activation, a transcription factor for iNOS.\textsuperscript{68} Treatment of streptozotocin-diabetic rats with a dose of 10 mg/kg body weight biochanin A decreased the plasma glucose and glycosylated hemoglobin and increased the plasma insulin and hemoglobin. It also decreased the activities of gluconeogenic enzymes (G6Pase, fructose 1,6-bisphosphatase) and increased the activities of GCK, glucose 6-phosphate dehydrogenase and glycogen contents in the liver of diabetic rats. Biochanin A or formononetin from red clover extract treatment significantly depleted lipids in diabetic mice due to down-regulation of hepatic APOC3 expression. This suggests that biochanin A or formononetin ameliorate the lipid profiles by activating PPARα.\textsuperscript{66,69} It showed antioxidant activity, inhibits β-cell apoptosis and promoting β-cell regeneration, insulin secretion, hepatic glycogen synthesis, and hepatic glycolysis and therefore could be used in the future as a new drug for T2DM treatment.

Isoflavones tectorigenin, tectoridin (PubChem CID: 5281810), irigenin (PubChem CID: 5464170), swertisin (PubChem CID: 124034) and their glucosides were isolated from the rhizomes of Belamcanda chinensis (Iridaceae), found to inhibit aldose reductase, an enzyme produce sorbitol in diabetics. IC\textsubscript{50} values for tectoridin and tectorigenin were found to be 1.08 x 10\textsuperscript{-6} M and 1.12 x 10\textsuperscript{-6} M. Both compounds significantly inhibited the sorbitol production in streptozotocin-induced diabetic rats at 100 mg/kg oral dose for 10 consecutive days and can be used for the prevention/treatment of diabetic complications.\textsuperscript{70} Tectorigenin (PubChem CID: 5281811) and kaikasaponin III (PubChem CID: 188384) were isolated from Pueraria thunbergiana (Fabaceae) flowers were reported for their potent hypoglycemic and hypolipidemic properties in the streptozotocin-induced diabetic rats. Moreover, tectorigenin and kaikasaponin III (PubChem CID: 188384) were found to be endowed with anti-oxidant potential and may contribute to ameliorate the streptozotocin-induced toxicity, T2DM and hyperlipidemia.\textsuperscript{71} Isoorientin (PubChem CID: 114776) isolated from water and butanol extracts of Cercropia obtusifolia showed significant hypoglycemic by activating insulin signaling pathways and reverting the insulin resistance in comparison to glibenclamide in diabetic rats.\textsuperscript{72}

**Flavonols:** Flavonols are widely dispersed metabolites in the higher plants. Moreover, these are dietary components. The well-known flavonols are kaempferol (PubChem CID: 5280863), myricetin (PubChem CID: 5281672), quercetin (PubChem CID: 5280343), fisetin (PubChem CID: 5281614), rhamnazin (PubChem CID: 5320945) and isorhamnetin (PubChem CID: 5281654) present in the daily foods. Fistein has been reported to have anti-diabetic and anti-oxidative properties. Oral administration of fistein (10 mg/kg body weight) in STZ-diabetic rats declined the blood glucose and glycosylated hemoglobin levels and increased the insulin levels. Expression of PEPCK and G6Pase (gluconeogenic) genes was
found to be decreased. Fistein treatment also reported to increase the activities of hexokinase, pyruvate kinase, and glucose-6-phosphate dehydrogenase through activation of AMPK (Figure 2). In parallel, it decreased the activities of lactate dehydrogenase, G6Pase, and fructose-1,6-biphosphatase. It also increased the hepatic glycogen contents and glycogen synthase activity and decreased glycogen phosphorylase activity.49 This is suggesting that it modulates the glucose homeostasis by modulating carbohydrate metabolism related enzymes.

Quercetin and its glycosides-rich extract of Vaccinium vitis-idaea (Ericaceae) were found to stimulate an insulin-independent AMPK pathway in muscle cells just like metformin. However, ATP synthase was reported to be inhibited only by quercetin, therefore aglycone quercetin was established to be responsible for AMPK activation. In another study, quercetin (20 µmol/L) was found to phosphorylate ERK1/2 that potentiates glucose and glibenclamide induced study, quercetin (20 µmol/L) was found to phosphorylate established to be responsible for AMPK activation. In another study, quercetin (20 µmol/L) was found to phosphorylate ERK1/2 that potentiates glucose and glibenclamide induced insulin secretion (Table 1). As per an another report quercetin activate Akt and AMPK that moderately neutralizes the effects of TNF-α and increase the basal and insulin stimulated glucose uptake C2C12 muscle cell lines. Quercetin was reported to significantly (p<0.02) increase in the activities of Na+/K+ ATPase and decrease (p< 0.01) sodium hydrogen exchanger (NHE) activity in T2DM. However, it was found to inhibit both when tested in vitro. Later on, it was observed that quercetin interact with L-type Ca2+ channels that stimulates insulin secretion by increasing Ca2+ influx at a site different from that of Bay K 8644. Quercetin, isoquercetin, and rutin (quercetin-3-O-rutinoside) were found to form complexes with α-glucosidases and inhibit the enzyme activity. Quercetin was found to be more potent inhibitor of α-glucosidases than that of acarbose. Postprandial hyperglycemia control is important in T2DM management and inhibition of α-glucosidases can reduce intestinal digestion of complex carbohydrates to glucose. In addition, quercetin and quercitrin were reported to inhibit cytochrome c release from mitochondria and attenuate mitochondrial apoptosis via the mitochondrial pathway and NF-κB signaling to prevent β-cell death (Figure 2). Therefore, quercetin/quercitrin protects cytokine-induced cell death, inhibited ROS as well as NO accumulation and improved glucose-stimulated insulin secretion due to reduced expression of inducible nitric oxide synthases (iNOS) and inhibited translocation of NF-κB.73–75 Conversely, quercetin was also reported to inhibit basal and insulin-induced phosphorylation of Akt, a downstream target of PI3K and therefore inhibit PI3K, in HT-22 cells. Dietary quercetin also impaired glucose tolerance. Oral quercetin reduced the respiratory quotient, suggesting that glucose utilization was impaired after treatment. The results obtained from one study also demonstrated that low doses of naringenin and quercetin acutely and potently impair glucose homeostasis.76 This effect may be mediated by inhibition of hypotalamic PI3K signaling.

Kaempferol, present abundantly in fruits and vegetables has been reported for various pharmacologic activities including anti-diabetic, hypolipidemic, anti-cancer, cardio-protective and anti-atherosclerosis. Recently, it was reported that hypolipidemic of kaempferol is due to stimulation of Sp1 by ERK1/2 and subsequent induction of LDLR expression. A number of studies have reported the decreased oxidative stress and increased glucose uptake in the cells treated with kaempferol or kaempferitrin (kaempferol-3,7-O-(alpha)-L-dirhamnoside). Kaempferol is reported to inhibit IRS-1, IκB kinase α, and IκB kinase β that reduce nuclear and cytosolic levels of NF-κB, TNF-α and IL-6 just like aspirin. Inhibition of NF-κB pathway reduces hepatic inflammatory lesions that improve insulin signaling defect in diabetes. It is also reported that kaempferol suppress the β-cell apoptosis, and improve the insulin synthesis mediated through activation of the cAMP/PPKA and PI3K/Akt pathways. One study demonstrated that kaempferol upregulates PKD-1, an important kinase in insulin signaling cascade, hence enhance PCK activity, GLUT-4 translocation, and anti-apoptotic protein expression. It was also reported that kaempferol treatment increases the GLUT-4, and AMPK expression impaired by high fat diet in mice. Gene expression analysis in response to kaempferol treatment showed that it decreased the expression of Pparγ, Cebpβ, Srebpl, Rxlβ, Lxrβ, Rora (adipogenic transcription factors) and Gpd1, Agpat2, Dgat2 (genes involved in triglyceride biosynthesis). It was also found to increase the expression of Tnfr1, Lsr, and Cel (lipolysis-related genes).49 Overall, kaempferol improves the hyperlipidemia and diabetes mediated through PI3K/GSK-3, cAMP/PPA and PI3K/Akt 1 pathways.

Myricetin, an omnipresent benzo-α-pyrole, has been shown very strong anti-oxidant property, twofold more than Vitamin E (D-α-tocopherol). But it was unable to protect vitamin E-deficient micosomes from lipid peroxidation. Myricetin (5 μM) produces Nrf2 mediated anti-oxidant response that efficiently inhibits NO and O2- produced in SIN-1-mediated DNA strands breakage. Along with anti-oxidative potential, myricetin exhibited strong anti-diabetic potential in rats fed with diet containing 60% fructose. It (1 mg/kg per injection, 3 times daily) significantly decreased the high glucose, triglyceride levels, insulin resistance and elevated the oral glucose tolerance. Myricetin increased the expression of IRS-1, p85 regulatory subunit of PI3-K basal phosphorylation of IR and IRS-1 and Akt therefore, improved the translocation of GLUT 4 in insulin-resistant soleus muscle. It suggests that myricetin enhances the insulin action on IRS-1-associated PI 3-kinase and GLUT 4 and therefore insulin sensitivity in insulin resistant soleus muscles (Figure 2). Results were also confirmed in another study where myricetin had excellent docking score with IR, EGFR, and AR/ER that further confirmed by MTT assay. It was found to down-regulate expression of IR, EGFR, mTOR, and Bcl-2 at transcriptional level. Beside the down-regulation of Bcl-2, myricetin was also modulating the TNF-α, interleukin 1β (IL-1β), and interferon γ (IFN-γ) therefore, preventing the β-cell death. Myricetin was reported to significantly decrease glomerulosclerosis and blood urea nitrogen, urinary volume and protein excretion. It also normalized the renal GPx and XO activities. Overall, myricetin, being a regular food ingredient and having high anti-
oxidative and anti-diabetic potential, could be used as a stand-alone drug or adjuvant to treat T2DM.

A patented formulation Emulin™ containing chlorogenic acid, myricetin, and quercetin was found to lower blood glucose levels significantly in T2DM group. However, emulin/metformin group was found to provide most significant blood glucose reduction by up to 20%.\(^8\) A concentration of 0.08 µM of myricetin-3-O-rhamnoside and europetin-3-O-rhamnoside isolated from Syzygium aqueum were reported to have insulin-like and insulin-sensitising effects on adipocytes. These compounds enhanced adipogenesis and 2-NBDG uptake and increase the adiponectin secretion in more efficient manner than rosiglitazone at all the tested concentrations.\(^8\) Leaves of Eugenia punicifolia (Kunth) DC. (Myrtaceae) were reported to contain myricetin-3-O-rhamnoside, quercetin-3-O-galactoside, quercetin-3-O-xyloside, quercetin-3-O-rhamnoside, kaempferol-3-O-rhamnoside, phytol, gallic acid, and trans-caryophyllene. In a study leaves extract was reported to decrease the glycosylated hemoglobin, basal insulin, thyroid-stimulating hormone, C-reactive protein, and systolic and diastolic blood pressure significantly.\(^8\) Resveratol and myricetin were reported to fail in prevention of cytokines-induced β-cell death in INS-1 (832/13) cells. However, quercetin or naringenin treatment decreased the INS-1 cell death by 40%. It was due to the downstream pAkt and pBad pathways activation. But both quercetin and naringenin didn’t show any effect on p-p38 MAPK, iNOS and MnSOD expression.\(^8\) None of these flavonoids were able to reverse the blunted glucose-stimulated insulin secretion after cytokines treatment. Hence, quercetin or naringenin possibly protect β-cells from cytokines toxicity through PI3-kinase pathway.

Pentamethylquercetin (PMQ) (Pubchem CID: 97332) is found in a variety of herbs and has potential as anti-diabetic agent. It is reported to reduce postprandial glucose and triglyceride levels by reducing insulin resistance, activating AMPK and increasing ACC phosphorylation and GLUT4 abundance. PMQ significantly activated the Akt/cAMP pathway and increased the expression of downstream memory-related proteins i.e. synaptophysin and glutamate receptor 1. PMQ was also reported to be potential candidate for treatment of obesity as it reversed the regulation of Sirt1, mTOR, 4EBP1, and S6K1, PPARγ, SREBP1, FAS, ATGL, HSL, and perilipin in the HF2-fed mice. Therefore, it was found to down-regulate Sirt1-mediated mTOR and adipogenesis signaling cascades and control obesity. Furthermore, PMQ down-regulates the TGF-β1, upstream Smad7 expression and inhibit Smad2/3 activation. Therefore, it suppresses TGF-β/Smad signaling and helps to ameliorate renal fibrosis in T2DM.\(^8\)–\(^8\) Isorhamnetin-3-O-galactoside from Oenanthe javanica was reported to suppress the release of HMGBl and therefore, the production of TNF-α and NF-κB activation.\(^8\) Quercetin, hyperoside, and isorhamnetin identified from methanol extract of Artemisia capillaris exhibited the α-glucosidase and PTP1B inhibitory activity, comparable to acarbose.\(^8\) Therefore, it might be helpful in treatment of vascular inflammatory diseases and secondary complication of T2DM.

Morin (Pubchem CID: 5281670) was reported to decline the TNF-α, IL-1β, IL-6 and lipid peroxides levels in animal models and cell lines. Possible target of morin may be SphK1/SIP signaling, results in reduced NF-κB activation and other inflammatory cytokines. It was also found to inhibit PTP1B and decrease the G6Pase, FDPase and increase the insulin levels.\(^9\) Therefore, it reduces the inflammation, increases the insulin sensitivity and could be beneficial in preventing T2DM. Rutin, another flavanoid, it could act in same way as morin. Additionally, it inhibits the expression of AGES, collagen IV and laminin, TGF-β1, p-Smad 2/3 p-Smad 7 and connective tissue growth factor was inhibited significantly. It was shown to increase glucose uptake mediated through PI3K, and MAPK pathways. Recently, it was reported to increase the brain-derived neurotrophic factor, NGF, and GSH, and reduced the level of TBARS levels. Moreover, it was exhibited anti-apoptotic activity as decrease caspase-3 levels and increases the Bcl-2 level in the diabetic retina.\(^9\)–\(^2\) Therefore, rutin has protective effects on events controlled by rutin myocardial dysfunction, oxidative stress, apoptosis, inflammation and T2DM.

**Flavon-3-ols:** Flavonols are the derivatives of flavans having 2-phenyl-3,4-dihydro-2H-chromene-3-ol skeleton. They exist as monomers or oligomers and present in fruits, foods, teas, and cocoa. Examples of flavonols include catechin, epicatechin (PubMed CID: 72276), epicatechin gallate (PubMed CID: 107905), epigallocatechin, epigallocatechin gallate (PubMed CID: 44134699), proanthocyanidins (PubMed CID: 21881649), theaflavins, thearubigins, procyanidin (PubMed CID: 107876), inulavosin (PubMed CID: 97820), and dihydromyricetin (PubMed CID: 161557).

**Cassia fistula** is a rich source of catechin, used in Indian medicine for diabetes treatment. Catechin was reported to reduce the blood glucose levels in Streptozotocin-induced diabetic rats. Catechin administration was found to increase tissue glycogen contents and restored the levels of GK, G6-Pase, GS and glycogen phosphorylase and GTUT-4 mRNA expression. Findings suggested that catechin acts as insulin mimetic. In another study, a catechin-rich beverage was found to be useful in obesity prevention and recovery of insulin secretory ability. (+) Catechin was also reported to increase the expression of adiponectin, PPAR-γ, FABP4, and LPL, the adipogenic markers, that promotes adipocyte differentiation and insulin sensitivity that reduce the T2DM risk. Catechin was also found to decrease the secondary complications of T2DM, like nephrotoxicity. It was reported as renoprotective and activity found to have equally effective as angiotensin-converting enzyme inhibitor, enalapril. It decreases the expression/activity of endothelin 1, lipid peroxidation, alanine transferase enzyme, and fibronecint. It also decreases the advanced glycation end products by regulating inflammatory pathway via methylglyoxal trapping. Catechin isolated from GMB-4 green tea was reported to prohibit the NADPH and NO decrease in endothelial cells induced by high glucose and attenuates the endothelial dysfunction in T2DM.\(^9\)–\(^9\)
(−)-Epicatechin is the active ingredient of cocoa and chocolates. It was also identified from Pterocarpus marsupium, a tree reported for antidiabetic properties in Indian traditional medicine. (−)-Epicatechin has been reported to produce insulinmimetic effects. It possesses the ability to scavenge ROS directly and also by modulating anti-oxidative defense system. Its reaction product is (−)-epicatechino-quinone. Reaction product o-quinone can also be generated through peroxidases. It was reported to inhibit macrophage migration inhibitory factor (MMIF), a molecule that maintain the inflammatory response. (−)-Epicatechin suppress the IL-1β mediates the T2DM pathogenesis that upregulate inducible form of nitric oxide synthase (iNOS) and NO production that cause damage to β-cells. It blocks the nuclear localization of p65 subunit of NF-κB and therefore IL-1β expression. Therefore, anti-T2DM effects of (−)-epicatechin are due to its anti-oxidant action and also because of non-antioxidant actions. (−) Epicatechin inhibits the TNF-α mediated transcription of MCP-1, interleukin-6, TNF-α, resistin, and protein-tyrosine phosphatase 1B involved in insulin signaling and inflammation. It also inhibits TNF-α mediated JNK, ERK1/2, NF-κB, p75 (NTR) signaling cascade and PPAR-γ expression. Catechin-rich green tea also reported to down-regulate G6Pase and fatty acid synthase, and the up-regulated of PPAR-α gene expression in the rats. Moreover, (−)-epicatechin reduce the advanced glycation end products and therefore diabetic retinopathy, secondary complications of T2DM.95,98,99 These finding suggest its role in management of insulin resistance and obesity (Figure 2).

Epigallocatechin gallate (EGCG) is among the most explored flavonoids. EGCG mechanisms for different types of activities have been described in some good reviews. It mainly target insulin signaling pathways where it affects the IRS2, Akt, FoxO1, PDX-1, mass and functional integrity of mitochondria. It reduces tyrosine-phosphorylation and increase levels of insulin receptor and IRS. It also inhibits PKC and activates the P13K/AKT pathway, AMPK, ERK1/2, p38 MAPK and increase GLUT-2 levels and glucose uptake in response to insulin. Moreover, EGCG has also been reported to control glucose homeostasis by reducing intestinal SGLT-1/GLUT2 ratio and thereby apoptosis. T2DM also causes stress along with nephropathy and neuropathy. NF-κB is the major transcription factor being target of oxidative stress, TNF-α, IL-1β, RAGE and MAPK. PCS were reported to decrease the MAPK and NF-κB and increase the IkB levels significantly. NF-κB activation inhibits insulin signaling through diacylglycerol and ceramide. NF-κB is a complex with IkB, an inhibitor protein in the cytoplasm. Stimulation from the above discussed factors phosphorylates IkB mediated by serine kinase cascade that leads to its degradation ubiquitination and facilitate NF-κB translocation to the nucleus. PCS treatment downregulated the gene controlled by NF-κB, i.e. pro-inflammatory cytokines, growth factors, adhesion molecules, COX-2 and iNOS. Activation of TNF-α, COX-2 and iNOS cause inflammation that lead to insulin resistance. Therefore, PCS terminates the inflammation caused insulin resistance. Moreover, PCS were also reported to reverse the SREBP-1 and SREBP-2 expressions in T2DM rat models.103,104,106,107 Overall, it can be concluded that PCS ameliorate hyperglycemic and hyperlipidemic condition through inhibition of NF-κB and regulation of inflammatory reactions (Figure 2).

Flavanones: Flavanones are the flavans with a 3,4-dihydro-2-aryl-2H-1-benzopyran-4-one skeleton. Some examples of from cytosol to mitochondria therefore, regulates mitochondrial transitional pore opening and oxidative and stress hence blocks cytochrome c release and caspase activity. EGCG also reported to and inhibit lipogenesis and enhance glycogen synthesis by phosphorylating AMP-activated protein kinase α and acetyl-CoA carboxylase expressions. Expression levels of mitochondrial fatty acid transporter carnitine palmitoyltransferase I (LCpt-1) were reduced by EGCG that also enhance insulin secretion from β-cells (Figure 2).97,100-102 Overall, EGCG exerts T2DM protective effects mediated through increased insulin sensitivity and anti-inflammatory actions. EGCG acts in the same fashion as metformin but, it is very difficult to achieve required physiological concentrations of EGCG, which limits it usage.

Hesperidin was reported for hypoglycemic as well for hypolipidemic properties. Studies suggest that hesperidin prevents hyperglycemia by increasing glycolysis and glycogen contents in STZ induced diabetic rats. Hesperidin treatment decreases HbA1c, glucose, LDL, TC, TG, and diastolic blood pressure significantly and increases LCAT and LPL level to a small extent. Hesperidin and naringin were reported to significantly ameliorated serum and liver MDA, NO and glutathione, and liver antioxidant enzyme and suppressed pro-inflammatory cytokines. Further, it was reported that hesperidin inhibit gluconeogenesis by inhibiting pyruvate transport to mitochondria, diversion of glucose 6-phosphate for glucuronidation and oxidation of NADH. It acts in a similar fashion to standard drug metformin in T2DM conditions. Hesperidin and its aglycone were also reported for their antioxidant, radical scavenging and anti-inflammatory activities. These were found to regulate caspasases, Bel-2, Bax, COX-2, matrix metalloproteinase-2 (MMP-2) and MMP-9 important in inflammation, apoptosis, angiogenesis and metastasis. It was found that hesperidin increases the Bel-2 and PPAR-γ expression and decreases the Bax expression significantly. It suggests its cardioprotective, anti-apoptotic and anti-oxidant potential. Hesperidin also reported to ameliorate the secondary complications of T2DM, such as neuropathy and retinopathy by increasing brain levels ofnorepinephrine (NE), dopamine (DA), and serotonin and inhibiting caspase-3, glial fibrillary acidic protein (GFAP) and aquaporin-4 (AQP4) expression. Neohesperidin, a similar compound significantly decreased 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 mice. It significantly inhibited the stearoyl-CoA desaturase 1 (SCD-1) and fatty acid synthase (FAS) gene expression and elevated hepatic AMPK phosphorylation. Therefore, neohesperidin may play an important role in T2DM and hyperlipidemia.

Naringin and naringenin, both flavanones studied extensively and reported to be useful in T2DM, hyperlipidemia and secondary complications induced by these disorders. Alam et al (2014) recently published a good review discuss the beneficial effects of these flavonoids. Naringin and naringenin act through AMPK activation and increase glucose uptake, improve glucose intolerance and insulin sensitivity. It also lowers the activities of G-Pase, PEPCK, DPP-IV and phosphorylation of p38 MAPK, ERK1/2, and JNK in the high-glucose-induced H9c2 cardiac cells. Further, these were reported to increase the expression of PPAR-γ that improves stimulates GLUT4 production, increase the IRS1 (Tyr162) phosphorylation that improves glucose homeostasis. It also increases the PPAR-α expression and therefore, expression of CPT-1 and UCP-2. At the same time it was reported to decrease the expression of liver X receptor (LXR), SREBP-1c, SREBP-1a, and hepatic 3-hydroxy-3-methyl CoA (HMG-CoA) reductase activity therefore, reduced the accumulation of lipid deposition in hepatic tissue. It also improves the mitochondrial compartment dysfunction. Naringin (5 µmol/L) was reported to reduce p38 and p53 phosphorylation, mitochondrial Bax and Bak expression, release of cytochrome c, and increase Bel-2 expression in high-glucose-treated (16.7 mmol/L) H9c2 cells. It also inactivated the caspase-3, -8, -9, MMP-9, and tissue inhibitor of metalloproteinase 1 (TIMP-1) and hence, prevented high-glucose-induced apoptosis in H9c2. It was reported to decrease the TNF-α levels and NF-kB expression and thereby inflammation, the secondary complication of T2DM. It was suggested that naringin activates Nuclear factor-erythroid 2-related factor 2 (Nrf2) that upregulates quinone oxidoreductase 1, GST P1, HO-1, and γ-glutamylcysteine ligase expression and decrease the expression of pro-inflammatory including TNF-α, COX2 and inducible NO synthase. Overall, naringin increase glucose uptake, reduces apoptosis, inflammation, fibrosis, and improve mitochondrial function. However, there is no clinical data till date on the effective dose of these flavonones to prevent or treat T2DM in humans.

Bavachin (Pubchem CID: 5321775) from the fruit of Psoralea corylifolia L. (Fabaceae) was reported for anti-hyperglycemic effect. It was found to increase plasma insulin and decrease blood glucose and TCH levels in T2DM rats. It was found to exert these effects by activating PPARγ, C/EBPa, increasing GLUT-4 translocation by activating Akt and AMPK pathways. It was reported to synergize with thiazolidinediones to induce PPAR transcriptional activity but use a different site in PPAR-γ and PPAR-α. In reporter gene assay, bavachin activated estrogen receptor (ER)-α and ER-β and these activities were completely inhibited by the pure estrogen antagonist, ICI 182,780. ERs are the important targets to treat T2DM. It was also reported to inhibit IL-6 induced STAT3 promoter activity in Hep3B cells and thereby control inflammation. Moreover, it was shown to decrease NF-kB and IκB-α kinase (IKK) activity and IκB-B degradation selectively. It was also increased the P65 and P50 translocation to nucleus and inhibited the IL-1 and therefore NF-κB and IκB-κB signaling pathways that attenuate the inflammation. Bavachin was also reported to be non-competitive inhibitor of Acyl-coenzyme A: cholesterol acyltransferase (ACAT) in HepG2 cells, an enzyme catalyzes cholesterol esterification important in cholesterol absorption from intestine (Figure 2).

Pinobanksin isolated and characterized from several plants was reported for to be a potent neuroprotective due to its anti-oxidative potential that lower the intra and inter cellular levels of AGEs. Korean Red Ginseng, a popular herbal medicine widely used to treat various kinds of diseases including diabetes. It was reported to contain pinobanksin-3-cinnamate, an active constituent. It was reported to inhibit TrxR1 in
Moreover, presence of insulin potentiates the glucose uptake in one hour of treatment ($p<0.01$) in a dose dependent manner. TNF-α peroxidation and prevent T2DM.\textsuperscript{124} Cells, a central protein in insulin signaling and down-regulate increase mRNA expression of PPAR-γ.\textsuperscript{125} It was reported to increase oxidative potential as reported in hesperidin. It was reported to eriodictyol (Pubchem CID: 440735) was reported to have anti-oxidant activity. A flavanone, diosmin (Pubchem CID: 5281613) initially isolated from Scrophularia nodosa L. abundantly present in the pericarp of citrus fruits has been shown to decrease HbA1c levels and increase GPx, SOD, and CAT activities. It was reported to increase the activities of hexokinase and G-6PDase and decrease the activities of G-6Pase and FDPase in STZ induced T2DM rats. It also reported to increase GST, vitamin C, vitamin E and reduce the lipid peroxidation. All the data shows that diosmin ameliorate the oxidative stress that increase the plasma insulin levels and prevent T2DM by regulating corresponding enzymatic activities.\textsuperscript{123} Another, flavanone, eriodictyol (Pubchem CID: 440735) was reported to have anti-oxidative potential as reported in hesperidin. It was reported to increase mRNA expression of PPAR-γ2 and adipocyte specific fatty acid binding protein. Moreover, it activates Akt in HepG2 cells, a central protein in insulin signaling and down-regulate TNFα, ICAM-1, VEGF, and eNOS, therefore decrease lipid peroxidation and prevent T2DM.\textsuperscript{124}

Liquiritigenin (Pubchem CID: 114829) and isoliquiritigenin (Pubchem CID: 638278), the flavanoidal compounds showed to affect the glucose uptake process. Both compounds were found to increase glucose uptake through influence to estrogen receptors which regulate the transcription processes of number of protein involved in glucose uptake and insulin sensitivity. Moreover, phenolic compounds have been reported to bind estrogen receptors and modulate their activity.\textsuperscript{125} It was observed that liquiritigenin and isoliquiritigenin treatment significantly increased the glucose uptake in C2C12 cells within one hour of treatment ($p<0.01$) in a dose dependent manner. Moreover, presence of insulin potentiates the glucose uptake in cell line. Therefore, liquiritigenin act as an agonist of estrogen receptors that module the expression of insulin sensitivity and glucose uptake genes at transcription level.\textsuperscript{125}

**Anthocyanins:** Anthocyanins are supposed to be in flavanol category, but two small changes i.e. a center ring contains a double bond between C2 and C3 and protonated oxygen, make it specific and its own sub-category. These changes in their structure also lead to quite different physiological effects. Anthocyanins are responsible for different colors in fruits and flora and widely distributed in human diets. More than 635 anthocyanins have been identified and received a considerable attention as natural coloring agents having anti-oxidative potential. Limitation of anthocyanins is their low bioavailability and unknown physiological mechanisms. Five major and well-studied anthocyanins are pelargonidin (PubChem CID: 440832), delphinidin (PubChem CID: 128853), malvidin (PubChem CID: 159287), peonidin (PubChem CID: 441773), and petunidin. Other anthocyanin found in nature are cyanidin (PubChem CID: 128861), apigenolin (PubChem CID: 441647), auranthinid (PubChem CID: 441648), 6-hydroxy-cyanidin (PubChem CID: 441697), leuteolinidin (PubChem CID: 441701), tracetidin, and hirustidin.

Pelargonidin was found various kinds of berries. It was found to be useful in hyperglycemia, oxidative stress, glycation of Hb. Pelargonidin was reported to inhibit phosphorylation of MAPKs i.e. p38, JNK and ERK1/2 and pro-inflammatory cytokines i.e. TNF-α, IL-1β, and eccl ligation and endothelial cell protein C receptor (EPCR) shedding.\textsuperscript{126,127} Hence, it was found to increase insulin secretion, β-cell regeneration, reduce insulin resistance, glucose resobation from GIT. Moreover, it was found to attenuate hippocampal MDA and increase catalase and AChE activities.\textsuperscript{128} Therefore, pelargonidin mitigate T2DM, oxidative stress, inflammation, cholinergic dysfunction and astrocyte reaction.

Cyanidin-3-galactoside was reported to inhibit intestinal α-glucosidase and pancreatic α-amylase. It was reported to inhibit α-glucosidase activity only in the upper region of the small intestine. It was also reported to prevent β-cells degeneration in STZ-induced diabetic rats, by increasing IR phosphorylation. DPP IV, one target to treat diabetes was also reported to be inhibited by cyanidin 3,5-diglucoside. Cyanidin was reported to increase expression of cholesterol efflux, ABCA1, and PPAR-α, PPARγ and C/EBPγ gene and decrease the expression of pro-inflammatory cytokines i.e. ICAM1, MCP1, and TGFβ1 in HK-2 cells (Figure 2). Moreover, it was found to activate NFκB, and inhibit LXR-α induced inflammatory response, these events lead to activation of Nrf2/EpRE pathway which helps to attenuate aortic lipid peroxidation.\textsuperscript{129-133} Guo et al, demonstrated reduced macrophage infiltration and MCP-1, TNF-α, and IL-6 levels and phosphorylation of FOXO1 through the AKT-dependent pathway. In addition, it activates Akt which phosphorylate FoxO1.\textsuperscript{132} Cyanidin 3-glucoside was reported to inhibit the phosphorylation of ERK and p38 without inducing the phosphorylation of JNK. It was also reported to regulate the expression of Bel-2 family, cytochrome c and caspase-3, the proteins related to intrinsic apoptotic pathway. It inhibit mitochondrial-mediated apoptotic pathway and reduce oxidative stress. It was also reported to significantly increased expression of PGC-1α, SIRT1 and UCP-3 genes.\textsuperscript{132,133} Taken together all these events, it was found to promote adipocyte differentiation, insulin sensitivity, prevent β-cell apoptosis, inhibits oxidative stress, and inflammation. Cyanidin-3-glucoside and pelargonidin-3-glucoside were also reported to decrease the Cyclin D1 expression and Erk1/2 and p38 MAPK activation, therefore, arrests the cycle at G1 stage.\textsuperscript{131}

Delphinidin and its derivatives possess anti-oxidant activity and found to be present in wide variety of fruits and vegetables. It was found to decrease the glycation rate and G-6Pase activity when administered with a dose of 100 mg/kg.\textsuperscript{134} Delphinidin-3-arabinoside was reported to increase HNF-1α expression which modulates DPP-IV and its substrate GLP-1 in caco-2 cells. It increase insulin secretion, up regulate insulin resistance
associated genes expression and proteins in pancreatic β-cells. GLP-1 secretion modulates I3P receptor-mediated intracellular Ca2+ mobilization through Ca2+-CaMKII pathway and therefore insulin secretion. A standardized formulation Delphinol® from maqui berries (Aristotelia chilensis) contains ≥25% delphinidins was reported to lower the post prandial blood glucose and insulin significantly by inhibition of sodium glucose co-transporter in small intestine.135–137 Further, delphinidin 3-O-beta-galactopyranoside-39-O-beta-glucopyranoside was reported to be the potent inhibitor of rat lens aldose reductase (IC50= 0.23 microg/mL), important enzyme to control retinopathy, a secondary of T2DM complications.136 Moreover, delphinidin chloride was reported to prevent endothelial cell function injury associated with T2DM and oxidative stress by inhibiting microvascular permeability and leukocytes adhering to the venular vessels.136

Malvidin and cyanidin in the black carrots (Daucus carota L.) were reported to increase the expression of CPT-1 and PPAR-α and decrease the expressions of FAS and SREBP-1c which decreased hepatic triglyceride levels significantly. These events increase the AMPK/ACC and AKT/FOXO1 signaling, therefore, prevents lipid and glucose metabolism exacerbation in OVX rats. Malvidin was also reported to decrease lipopolysaccharide-induced NF-κB, poly ADP-ribose polymerase and MAPK activation. It also prevents ROS production and mitochondrial depolarization therefore, found to be useful in diabetes, hyperlipidemia, hypertension and cardiovascular disease.136,137 Some reports claimed the higher activity of anthocyanins as compare to standard drugs glibenclamide and metformin.

Anthocyanin isolated from Aornia melanocarpa was reported to improve 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.141 Yoo and colleagues isolated 2,3-dioxygenated flavanone, erigeroflavanone (Pubchem CID: 24850296) from flowers of Erigeron annuus (Linn.) Pers. showed inhibitory activity against advanced glycation with IC50 value of 22.7 μM.142 Shamim isolated from Bombax ceiba Linn. showed significant reduction in hyperglycaemia in Sprague-Dawley rats.143 Flavonoids, kakonein (Pubchem CID: 5281807) isolated from root of Pueraria lobata (Willd.) Ohwi reported to lower blood glucose level of alloxan or adrenalin-induced diabetic mice.142 Ohwi showed potent hypoglycemic and hypolipidemic effects of tectorigenin isolated from flowers of Pueraria thumbergiana (Willd.) in the STZ-induced diabetic rats.145 Therefore, limited number of studies and being regular components of food products, these compounds need further studies to explore their in vivo antidiabetic effects.

PHENOLICS

Non-flavanoid phenolics contain hydroxycinnamic (C6C3) and hydroxybenzoic (C6C1) constitutive carbon frameworks. These non-flavanoid phenolics can be divided into four different groups i.e. phenolic acids, quinines, stilbenes, and coumarins. Phenolics are well known compounds possess antimicrobial and antifungal activities. However, they were also investigated for their nutritional values and also for their anti-diabetic efficacy. These were found to have anti-inflammatory activity in different T2DM models by reducing IL-1β, IL-8, MCP-1, and COX-2 or iNOS production. Some phenolics were also reported to prevent secondary complication of T2DM, such as retinopathy, cardiopathy and nephropathy. Phenolics are present in human foods and also human studies with pure compounds or diet enriched with specialized phenolics are very rare therefore, new studies are needed to confirm their beneficial effects.

Phenolic Acids: This class of compounds includes the derivatives of benzoic acid. Hydroxybenzoic acid, cinnamic acid, gallic acid, ellagic acids, caffeic acid, ferulic acid and p-coumaric acids are major compounds of class. 4-Hydroxybenzoic acid was found to increase peripheral consumption and therefore, decreased the plasm glucose levels without affecting serum insulin and liver glycogen contents. Hydroxycinnamic acid derivatives i.e. cinnamic acid (Pubchem CID: 637542), p-coumaric acid (Pubchem CID: 637542), caffeic acid (Pubchem CID: 689043), ferulic acid (Pubchem CID: 445858), chlorogenic acid (Pubchem CID: 1794427), and rosmarinic acid (Pubchem CID: 5281792) possess potent antioxidant and anti-inflammatory properties. These derivative were reported to inhibit macrophage infiltration and NF-κB activation, reduce the expression of TNFα, MCP-1 and plasminogen activator inhibitor type-1 (PAI-1). These derivatives also prevent adipocyte differentiation and lower the lipid profile in experimental animals. Therefore, these derivatives are useful in diabetes, hyperlipidemia and obesity.146 Active compound anacardic acid (6-pentadecylsalicylic acid) (Pubchem CID: 167551), was reported as COX inhibitor. Anacardic acid was isolated from Anacardium occidentale Linn. (Cashew nut tree). It activates AMPK that increase GLUT-translocation to cell membrane and increase glucose transport into C2C12 myotubes in a concentration-dependent manner (Figure 3).147 Cinnamic acid also reported to normalize the lipase and angiotensin-converting enzyme (ACE) in high fat diet-rats and increase the diameter of aorta and aortic arch and avoid vasoconstriction. Cinnamic acid was also reported to inhibit HMG-CoA reductase and ACAT activities in high cholesterol fed rats, hence reduced the TG and cholesterol levels. It was reported to stimulate the adiponectin secretion and AMPK phosphorylation, therefore improved the insulin sensitivity comparable to standard drug glibenclamide. It was also found to improve liver steatosis and kidney indices of toxicity. Cinnamic acid derivative i.e. hydroxycinnamic acid were also reported to inhibit the PTP1B a major negative regulator of insulin signaling pathway.146 Therefore, it exhibit anti-diabetic, anti-obesity and anti-hypertension properties (Figure 3).
Gallic acid (PubChem CID: 370) (10-30 µM) was reported to increase the expression and secretion of adiponectin by increasing the adipocyte differentiation. It was found to increase the expression of PPAR-γ target proteins and fatty acid binding protein-4. Gallic acid and its derivatives were found to reduce depressive symptoms and oxidative stress significantly. These findings suggest that gallic acid exerts anti-diabetic effects through adipocyte differentiation and scavenging the free radicals and peroxynitrite. Caffeic acid (10 mM) was reported to modulate Nrf2 expression and therefore, induce the nuclear translocation of NF-κB and the downstream expression of endothelial adhesion molecule 1 and restores antioxidant levels by upregulating Nrf2/EpRE pathway in human endothelial cells exposed to 25 mM glucose (Figure 3). It was also observed that caffeic acid affects the apoptosis pathway by downregulating the expression of caspase enzymes and increasing the Bcl-2 phosphorylation in high glucose treated cells. Caffeic, chlorogenic, ferulic, p-coumaric and cinnamic acids were reported to inhibit triglycerides accumulation in Hepg2 cells and therefore, useful to treat non-alcoholic fatty liver disease. Ferulic acid was also reported to act in same manner as caffeic acid and up-regulate the expression of Nrf2 and inhibit the expression of TNF-α and IL-1β by inhibiting the activation of NF-κB in dose dependent manner and prevent the cell apoptosis and decrease the oxidative stress. Ferulic acid treatment also increases the glucose uptake, insulin sensitivity, and tolerance in T2DM animal models. It was found to decrease the activity of GS, GK and increase the activity of PEPCK and G-6Pase and restore the glucose levels in a similar fashion of metformin. Moreover, ferulic acid and feruloylated arabinoxylan mono/oligosaccharides were reported to inhibit GLUT-2 expression by impairing the interaction between SREBP1c, HNF1α, HNF3β and GLUT2 gene promoter and modulate GLUT-4 activity. Ferulic acid was reported to have anti-diabetic properties and significantly reduced the glycated hemoglobin (HbA1c) and lipid peroxidation. It was reported to increase Na+/K+-ATPase level in high glucose treated rats, hence prevents T2DM. It was also reported to reduce oxidative stress by inhibiting protein carbonylation in GSH-depleted hepatocytes and can be used to inhibit or decrease glyoxal and methylglyoxal induced hepatotoxicity. Overall, ferulic acid improves insulin sensitivity, hepatic gluconeogenesis, and inhibits gluconeogenesis, and oxidative stress to maintain glucose homeostasis in T2DM condition.

*p-Coumaric acid (PubChem CID: 637542) 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. At the same time, it was reported to decrease the cholesterol and triglyceride levels in plasma. It was also reported to inhibit TNF-α mediated increase
in MCP-1, PAI-1 and ROS in adipocytes. Therefore, it increased the secretion of adiponectin, expression of SOD, GSH, GPx and GST in TNF-α treated adipocytes. Moreover, LD50 was very high and therefore, an increased dose may increase the biological activates. However, its low intestinal absorption is a disadvantage in its utilization.\textsuperscript{136,152} Chlorogenic acid (PubChem CID: 1794427) exhibited negative associations with fasting blood glucose, glycated hemoglobin and C-reactive protein. As, in case of other phenolics, it also reduces the HMG-CoA reductase activity and increases LPL activity in plasma hence reduces the plasma cholesterol and triglycerides levels. It was reported to stimulate glucose transport in skeletal muscle comparable to the anti-diabetic drug rosiglitazone by increasing the GLUT 4 translocation and of AMPK and Akt phosphorylation (Figure 3).\textsuperscript{149,153,154} Marsupin (PubChem CID: 134369) was identified from heartwood of \textit{Pterocarpus marsupium} Roxburgh. It was reported to significantly decrease glucose levels in diabetic rats as compared to metformin by modulating tissue glucose utilization in tissues, reducing the glucose absorption from the gastrointestinal tract and improving insulin and pro-insulin levels.\textsuperscript{125,155}

Luo et al (1998) reported that masoprocol (PubChem CID: 71398) isolated from \textit{Larrea tridentata} (DC.) decrease plasma glucose to 8 mmol/L in male C57BL/ks-db/db or C57BL/6J-ob/ob mice models of T2DM.\textsuperscript{156} Masoprocol is a potent inhibitor of lipoygenase, formyltetrahydrofolate synthetase, carboxylesterase, and cyclooxygenase. It also has antioxidant activity. The moracin M (PubChem CID: 185848), steppogenin-4′-O-glucoside and mullberroside A identified from root bark of \textit{Morus alba} (Linn.) were found to be endowed with in vivo hypoglycemic effect in alloxan-diabetic mice.\textsuperscript{157}

**Quinones:** Quinones are ubiquitous class of compounds present in natural products or generated through metabolism of hydroquinones or catechols. These are highly reactive and as result generate superoxide anion radicals. The generation of ROS is responsible for their toxic and antimicrobial nature. Quinones mainly studied for their antimicrobial activities and a few compounds were studied for other kinds of biological activities. \textit{Rheum emodi} contains 1,8-dihydroxynaphthoquinones, i.e. rhein (PubChem CID: 10168), emodin (PubChem CID: 3220), chrysophanol (PubChem CID: 10208) and physcion (PubChem CID: 10639). All the quinones from the plants exhibited good anti-T2DM activity where emodin was best to decrease the blood glucose and inhibited the α-glucosidase activity better than acarbose. Embelin, a quinone derivative, found in \textit{Embelia ribes} Burm (Myrsinaceae) has been reported for anthelmintic, anti-tumor, anti-diabetic, anti-bacterial and anti-inflammatory activities. Several studies have shown that the anti-inflammatory activity of embelin is mediated by reduction in TNF-α by inhibiting TNF-α converting enzyme.\textsuperscript{158,159} Anti-inflammatory compounds also reported to increase insulin sensitivity and help to ameliorate secondary complications of T2DM.

**Stilbenes:** Stilbenes are produced in plants in stress conditions. It represents a small class of secondary plant metabolites having two aromatic rings linked by an ethane bridge. Resveratrol (PubChem CID: 445154), pterostilbene (PubChem CID: 5281727), piceatannol (PubChem CID: 667639), lonchocarpene (PubChem CID: 6443491) and 3,5-dimethoxy-4′-O-aryl-trans-stilbene are the representative of the this group. Most studied molecule of this group is resveratrol, comprehensively reviewed by Tomasz Szukiedelska and Katarzyna Szukiedelska (2015).\textsuperscript{160} Resveratrol (3,5,4′-trihydroxystilbene) was mainly found to be useful in aging, inflammation and oxidative stress. Resveratrol was reported for neuroprotective effects through modulation of AMPK, SIRT1, and PGC-1α expression via LKB1. Resveratrol reversed insulin resistance and increased expression and translocation of GLUT4 in C2C12 cells. Increased insulin sensitivity was attributed to increased activities of IRS-1, Akt, and PI3K. Modulation of PGC-1α expression decreased the expression of FAS, ACC and CPT-1.\textsuperscript{60,160} Hence, it was reported to influence lipid metabolism along with glucose. In the contrary, Ho et al., (2010) didn’t find it neuroprotective but suggested its beneficial effects in T2DM.\textsuperscript{161} Same pathway modulation is useful to prevent T2DM and its secondary complications (Figure 2 and 3). Studies reported that resveratrol and glargliclaze significantly reduced both blood glucose levels and HbA1c levels (p<0.001) in adult male \textit{Wistar albino} rats treated with STZ. Both enhanced the activities of hexokinase, G-PDase, F-1, 6 BPase, pyruvate kinase, and G-6Pase. However, another study reported that resveratrol was not as effective as gliclazide in improving T2DM conditions and dose response profile remains intermediate. In a study, resveratrol was reported to improve intra-cavernous pressure and mean arterial blood pressure as compared to T2DM rats. It was reported to inhibit phosphodiesterase-5 expression and increase nNOS and eNOS expression and effective to control ROS production. Simultaneously, it was reported to increase cavernous cGMP levels. Therefore, mechanism to control blood pressure and T2DM was attributed to upregulated NO-cGMP, AMPK/SIRT1 signaling pathways and anti-oxidative properties. The acute treatment of resveratrol inhibits the mitochondrial F1 ATPase that activates AMPK independent from SIRT1 and mediated through AMP. In addition, resveratrol was reported to inhibit ATP-sensitive and voltage-gated K+ channels and activate Ca2+-regulated K+ channels in the MIN6 cells that increase the insulin secretion significantly (Figure 2).\textsuperscript{160,162} In spite of a number of studies, clinical trials of resveratrol in T2DM are controversial.

Pterostilbene (3, 5-dimethoxy-4′-hydroxy-trans-stilbene) (PubChem CID: 5281727), a dimethyl ether derivative of resveratrol is more stable than resveratrol. Pterostilbene (PubChem CID: 5281727) was initially isolated from the heartwood of \textit{Pterocarpus marsupium}. Pterostilbene increases the GLUT-4 protein expression and Akt phosphorylation for its efficient translocation and therefore, increases glucose uptake (Figure 3). It was observed that pterostilbene increases cardiotropin-1 that mediates Akt phosphorylation. Additionally, treatment with pterostilbene also increased GK activity selectively. Isoliquiritigenin and pterostilbene were also found to structural analogues of estrogen receptor agonists, an indirect target to increase insulin sensitivity.\textsuperscript{163,164} Lonchocarpene and
3,5-dimethoxy-4′-O- prenyl-trans-stilbene (DPS) were reported to inhibit \(\alpha\)-glucosidase (\(pIC_{50} = 5.68 \pm 0.12\) and 5.73 ± 0.08). Moreover, DPS was found to increase oral tolerance. Therefore, DPS may have a potential to treat T2DM.\(^{166}\) Two prenylated stilbenes namely denticulatains A and B, isolated from the fronds of *Macaranga denticulata* exhibited inhibitory activity against AChE, at a concentration of 50 \(\mu\)M.\(^{166}\) Further studies are required to explore the anti T2DM activities of these stilbenes, if there is any. Two compound namely, piceatannol and scirpusin B was identified from stem bark of *Callistemon rigidus* R. Br. These compounds were reported to inhibit \(\alpha\)-amylase activity in mouse plasma and decreased the postprandial blood glucose level.\(^{167}\)


Coumarin was reported to deplete plasma glucose and lipid peroxides and increase the plasma insulin and antidiabetic enzymes significantly in the STZ-nicotinamide (NA)-induced T2DM rats. Oral doses of 100mg/kg body weight per day for 45 days coumarin significantly decreased the plasma glucose, HbA(1)c, G-6PDase levels and increase the of insulin, hemoglobin, G-6Pase, and F-1,6-BPase levels in STZ-NA-induced diabetic rats.\(^{168}\) Esculin (PubChem CID: 5281417), a well-known coumarin was reported to decrease TG, CH, LDL, IL-1, IL-6, ICAM-1, NO and NGAL levels in a dose dependent manner in serum of STZ-induced diabetic rats. It also significantly reduced AGEs significantly after the dose of 30 and 90 mg/kg in diabetic rats. Authors link the hydropelicid and anti-inflammatory activities to the inhibition of AGEs formation in STZ-induced diabetic rats.\(^{169}\) Cinnamom (PubChem CID: 6850781), a compound isolated from *Cinnamomum* species was reported to modulate PK, PEPCK, PPAR-\(\gamma\) and intestinal glucosidases activities through modulation of IR phosphorylation, GLUT-4 synthesis and translocation. Clinical trials with cinnamon dosing 500 mg to 6 g/day were found to control hyperglycemic conditions and reduced the blood glucose I and Hba1c levels.\(^{167,170}\) The asinensins A and B specifically phosphorylate AMPK and therefore increase the GLUT-4 translocation from cytosol to membrane and increase glucose uptake activity as indicated that compound C (AMP-activated protein kinase inhibitor) inhibits theasinensin-stimulated glucose uptake in L6 cells. Moreover, its specific phosphorylation of AMPK was also confirmed by using CaM KK inhibitors that blocked the glucose uptake by inhibiting GLUT-4 translocation.\(^{171}\) Overall, theasinensins activates CaMKK/AMPK pathway and not PI3K/Akt pathway (Figure 3).

Cinnamaldehyde, a active component derived from Cinnamom has been reported to increase glucose uptake and insulin sensitivity in skeletal muscles and adipose tissues in diabetic animals. It has been reported to act on AMPK, RBP4-GLUT4, PPARs, PI3K/IRS-1 and TRPA1-grehlin pathways, thereby improving diabetic effects. It has also been found to regulate PTP1B and amylose activities.\(^{172}\)

Further six coumarins namely, 4-hydroxy Pd-C-III, 4′-methoxy Pd-C-I, decursinol, decursidin, umbelliferone 6-carboxylic acid, and 2′-isopropyl psoralene isolated from *Angelica decursiva* containing nodakenin, nodakenetin, umbelliferone, cis-3′-acetyl-4′-angelylkhellactone, 3′(R)-O-acetyl-4′(S)-O-tigloylkhellactone, isorutarine and para-hydroxybenzoic acid exhibited potent inhibitory activities against \(\alpha\)-glucosidase, PTP1B, rat lens aldose reductase (RLAR), AChE, BChE, and \(\beta\)-site amyloid precursor protein cleaving enzyme 1 (BACE1) (Figure 3).\(^{173}\) Further six coumarins namely, 4-hydroxy Pg-C-III, 4′-methoxy Pg-C-I, decursinol, decursidin, umbelliferone 6-carboxylic acid, and 2′-isopropyl psoralene isolated from *Angelica decursiva* inhibits PTP1B and \(\alpha\)-glucosidase activities in ranges of 5.39-58.90 \(\mu\)M and 65.29-172.10 \(\mu\)M (IC50s), respectively. Moreover, these coumarins suppressed ONOO (-)-mediated tyrosine nitration effectivly in a dose-dependent manner.\(^{173}\) Umbelliferone, alone was reported to normalize the levels of glucose, sialic acid, total hexoxes, fucose, and hexosamines in STZ-diabetic rats, thereby reduced the glycoprotein formation. Umbelliferone also decrease the levels of blood glucose and lipid peroxidation markers and nonenzymatic antioxidants (Vitamin C and GSH).

On the other hand, it elevated levels of vitamin E, enzymatic antioxidants SOD, CAT, GPx, and G-PDase activity and altered the lipid profile in erythrocytes of STZ-T2DM rats.\(^{175}\) Results concluded that umbelliferone is a promising agent for T2DM, oxidative stress and hyperlipidemia (Figure 3).

Skimmin, a coumarin from *Hydrangea paniculata*, was reported to decrease the Scr and glucose levels and increase the creatinine clearance significantly in the same way as standard drug losartan-treated rats. Skimmin significantly decreased the glomcrulus segmented sclerosis and incidence of tubule vacular degeneration in better way than losartan. It was found that skimmin down-regulated renal fibrosis through down-regulation of TGF-\(\beta\)1 and TGF-\(\beta\) Receptor I expressions.\(^{176}\)

Osthole (50 \(\mu\)M) moderately increase the glucose uptake in L929 cells but block full activation of glucose uptake even in presence of most robust activators of glucose uptake. The behavior of osthole was equivalent to thiol compounds and probably interacts with cysteine residue of GLUT-1.\(^{177}\) Other coumarins including umbelliferone, coumarin, and 7-methoxy coumarin were reported not to affect the glucose uptake in the same report. Aculatin, a coumarin isolated from *Toddalia asiatica* (L.) Lam. enhanced pre-adipocyte differentiation indicated by increased cellular TG levels and G-6PDase activity. It increased the expression of PPAR-\(\gamma\) controlled genes i.e. Pparg, Ap2, Cd36, Glut4 and Adipoq indicates adipogenesis.
activity. Finally, it was found to increase glucose uptake and lipolysis.

Total coumarins from *Urtica dentata* Hand were reported to be reno-protective in T2DM nephropathy. It was found to inhibit high glucose-induced HBZY-1 cell proliferation and hypertrophy mediated through TGF-β1, connective tissue growth factor, and TLR 4 modulation. Findings were correlated with T2DM rat model where it reduced TGF-β1, connective tissue growth factor, and TLR-4 expression in the kidneys and therefore, increased body weight, reduced morphological evidence of renal pathology; blood glucose, urea nitrogen levels, albuminuria, and serum creatinine. Methanolic extract of *Clausena anisata* (Wild) Hook [family: Rutaceae] root contains terpenoid and coumarins were reported to stimulate pancreatic β-cells and secretion of insulin. Fraxidin, a coumarin was identified using in vivo bioassay-guided fractionation *Teramnus labialis* (Roxb.) Benth. (Fabaceae) extract is found to be responsible for hypoglycemic activity in C57BL/Ks-db/db mice model of T2DM. Nordentin (PubChem CID: 5320206), a coumarin from *Clausena harmandiana* has been reported to significantly increase the glucose uptake activity in L6 myotubes in dose dependent manner.

**Xanthones**: Xanthones are the polyphenols and closely related to the flavonoids. Xanthone backbone has two benzene rings attached with carbonyl group and oxygen that restrict the free rotation about the carbon-carbon bonds. The unique backbone and position of the chemical groups defines the specific properties of xanthones. Xanthones are reported to have several types of biological activities including antidiabetic properties. Mangostins (PubChem CID: 5281650), swerchin (PubChem CID: 5281660), mangiferin (PubChem CID: 5281647), norathryiol (PubChem CID: 5281656) and cudracrassicxanthone (PubChem CID: 44592062) are example of this category. Other natural xanthones are α-mangostin and γ-mangostin (PubChem CID: 5281650), 3,5,6,8-tetrahydroxyxanthone-1-C-β-D-glucoside, 3,4-dihydroxyxanthone-1-O-(β-D-glucoside), and 3,4,7,8-tetramethoxyxanthone-1-O-(β-D-glucoside) etc.

Mangiferin (PubChem CID: 5281647) isolated from *Mangifera indica* (Anacardiaceae) and widely distributed in higher plant has been reported for anti-diabetic as well as anti-hyperlipidemic properties. Indian system of traditional medicine, also reported the use of *M. indica* bark to treat diabetes. It was reported to decrease blood glucose level in KK-Ay mice model of T2DM by increasing insulin sensitivity. Administration of 10 and 20 mg/kg mangiferin intraperitoneally for 30 days decreased FBS, TC, TG, LDL, and VLDL levels significantly (P<0.05) and elevated HDL levels in T2DM rats. Moreover, it was found to inhibit α-amylase (IC50 value 74.35±1.9μg/ml) and α-glucosidase (IC50 41.88±3.9μg/ml) as compared to acarbose (IC50 83.33±1.2μg/ml) (Table 1). Mangiferin also reported to decrease in glycosylated haemoglobin and CPK levels significantly and ameliorate oxidative stress comparable to insulin treatment. Norathryiol, a xanthonel aglycone, similar to mangiferin, except for a C-glucosyl bond, was reported to improve the glucose utilization and insulin sensitivity through up-regulation of AMPK phosphorylation. Norathryiol was also supposed to be active metabolite of mangiferin. Therefore, mangiferin may have beneficial effects in the T2DM management. A derivative of mangiferin namely mangiferin X-3, a xanthonoid, increased glucose uptake and AMPK phosphorylation in 3T3-L1 cells. It phosphorylate AMPK by both ways i.e. LKB1-dependent and -independent manner. It also activated the AMPK downstream target, acetyl-CoA carboxylase (ACC) in the hypothalamus, liver, adipose and muscle tissues (Figure 3).

Saxena et al (1991) showed significant blood sugar lowering effect of swerchin (Pubchem CID: 5281660), isolated from *Swertia chirayita* (Roxb. ex Fleming) in healthy and STZ induced diabetic rats. It appears to improve insulin resistance by enhancing insulin signaling. Methylswertianin derivatives of xanthone isolated from *Swertia Punicea* Hemsl. showed good antidiabetic activity in STZ induced diabetes. Bellidifolin (Pubchem CID: 5281623) was reported to reduce fasting blood glucose levels, fasting serum insulin and improve the oral glucose tolerance. Bellidifolin along with methylswertianin also depleted the TC, LDL and TG levels and increased relative HDL concentrations. These compounds are found to increase the expression of insulin-receptor alpha subunit (InsR-alpha), IRS-1, and PI3K. Both the compounds also increased the hepatic glycogen and increased the activities of GK, G6-Pase. Resultant improvement in insulin resistance by enhancing insulin signaling was observed. Cudracrassicxanthone A (Pubchem CID: 11153672), an isoprenylated xanthone prevents NF-κB and JAK/STAT activation, cytokines-induced NO production, iNOS expression, and inhibits glucose-stimulated insulin secretion. It was also reported to prevent functional β-cell damage.

1,3,7-Trihydroxyxanthone (Pubchem CID: 5281635) and 1,3-dihydroxybenzoxanthone (Pubchem CID: 5281631) were reported to be noncompetitive inhibitors of α-glucosidase through inducing a loss in the α-helix content of α-glucosidase. Both are reported to bind with different sites therefore, have significant synergetic inhibition to α-glucosidase, which provide clues that synergetic inhibition can be promising strategy to treat T2DM. 1,8-Dihydroxy-3,5-dimethoxyxanthone (Pubchem CID: 5281653), 1-hydroxy-3,5-dimethoxyxanthone (Pubchem CID: 5488808) and 1-hydroxy-3,7,8-trithoxyxanthone, isolated from *Canscora lucidissima* were reported to increase the rate of myocardial cells and membrane fluidity and decrease the release of LDH. This suggests the protective effects of myocardium by preventing the anoxia/reoxygenation damages.

**Triterpenes**

Triterpenes are formed through the squalene epoxide arrangement followed by condensation. These secondary metabolites in plants play an important role in their defense. Triterpenes are reported for their diverse kinds of biological activities in animals. Triterpenoids have structural similarity
with steroidal hormones, therefore, their mechanism of action are speculated to regulate gene expression under control of glucocorticoid responsive elements (GRE). Binding with GRE suppress pro-inflammatory and enhance anti-inflammatory proteins expression. Moreover, being lipophilic in nature, these bind with cell membranes and affect their fluidity. Binding capability of triterpenes with cell membranes also ensure their less bio-availability. Hence, major limitation of triterpenoids was reported to be their movement into the cells being large molecules and their lipophilic nature. However, on the contrary, triterpenoids were found to cross the cell membranes as well as blood brain barrier. Higher intake of triterpenoids increases their bioavailability and accumulates them in liver, circulation and other tissues. Therefore, major activity and effects of triterpenoids is due to their anti-inflammatory properties. Later on, to increase the bioavailability of triterpenes, their combination with cyclodextrins were tested and found to have an increased bio-availability.190 Broadly, terpenes can be classified into pentacyclic, tetracyclic and acyclic triterpenes. In the current review, recent studies on terpenoids will be included with their mechanism of actions.

**Pentacyclic triterpenes**: Pentacyclic triterpenes are most abundantly present terpenes in the nature, mainly in higher plants. These can be classified as oleananes, ursane, lupane, hopane and gammacerane. Oleanolic and ursoic acids (PubChem CID: 64945) are good examples of oleananes and ursanes.

**Oleananes**: Oleanolic acid (PubChem CID: 10494) was reported to bind with GRE or muscarinic M3 receptors in pancreatic β-cells that results in anti-inflammatory response and increases arachidonic acid secretion. Later on it was reported to decrease adrenaline induced plasma glucose levels and inhibit the IFN-γ induced NO production in mouse macrophages. It was also reported to attenuate the phosphorylation of Akt, mTOR, p70s6k, S6, GSK3β, and FoxO3a as well as inhibits the MEK kinase (Figure 4). Results indicated the inhibition of Akt/mTOR pathway and therefore, cardiac hypertrophy. On the contrary, oleanolic acid when prescribed with metformin was shown to increase the phosphorylation of AKT, PI3K, AMPK, and ACC and therefore, help GLU-4 translocation and increase insulin sensitivity. Moreover it was reported to decrease the protein expression levels of G-6-Pase, PEPCK1, and TORC and reduced the mTOR and CREB phosphorylation. Oleanolic acid was also reported to inhibit α-glucosidase enzyme in a concentration-dependent manner which was higher that standard antidiabetic drug acarbose.191 Oleanane-type triterpenene bartogenic acid (PubChem CID: 45272347), isolated from seeds of *Barringtonia racemosa* (Lecythidaceae), exhibited moderate inhibitory activity against α-amylase and α-glucosidase with IC50 168.09 µg/mL.190 Glycyrrhizic acid (PubChem CID:14982) treatment has been 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 (Figure 4).193 α-Amyrin (PubChem CID: 73170) isolated from aerial root of *Ficus bengalensis* Linn. reported to have hypoglycaemic activity in normal and db/db diabetic rat and significantly improved the diabetic condition in STZ induced diabetic rats. The mechanism of action reported is related to its protective/inhibitory action against the insulin degradative processes.194 *Hemidesmus indicus*, contains β-amyrin palmitate (PubChem CID: 13915599) reported to have remarkable anti-hyperglycemic activity at a very low concentration (50µg/kg body weight) probably by blocking the entry of glucose from the intestine.194 Oral administration of friedelan triterpenoid, 4-oxa-3, 4-secofriedelan-3-oxic acid (Pubchem CID: 44593506) (3 mg/kg) isolated from *Quercus suber* L. in STZ-induced diabetic Sprague Dawley rat reduced the total body weight, serum glucose level and ALP, AST and AST activities, and restored the antioxidant status of liver.195 Friedelane-type triterpene salasones A (Pubchem CID: 21589703), B (Pubchem CID: 21589704) and C (Pubchem CID: 21589705) and norfriedelane-type triterpene, salaqunone A and acylated eudesmane-type sesquiterpene, salasol A (Pubchem CID:11092680), isolated from the aqueous methanolic extract of *Salacia chinensis* Linn. showed inhibitory effect on rat lens aldose reductase.196 The new colecan-13-ene-type triterpene, centellasapogenol A (Pubchem CID: 15508087) isolated from methanolic extract of *Centella asiatica* Linn. reported to inhibit aldose reductase.197 Arjunoic acid (Pubchem CID: 11504083) identified from the bark of *Terminalia arjuna* was reported to be anti-oxidant.198 It also inhibited the intracellular RNS and ROS formation in spleen tissue, polylol pathway. It was also found to increase the IL-2 and IFN-γ levels and decreased the TNF-α level, probably due to the anti-oxidant potential (Figure 4).199

**Ursane**: Mixture of ursolic (Pubchem CID: 64945) and oleanolic acids isolated from *Phyllanthus amarus* (Euphorbiaceae) was found to have IC50 4.41 µM against porcine pancreatic α-amylase. Another study, showed that *Melaleuca leucadendron* endowed with ursolic acid inhibit PTP1B, α-glucosidase and formed new blood vessels in retinal tissue by decreasing the expressions of VEGF, COX-2 and MMP-2. Ursolic acid was also reported to inhibit hypertrophy and proliferation through down-regulation of PI3K, Akt, mTOR, SQSTM1, and collagen I expression and up-regulated LC3II expression in HG-induced mesangial cell. It was also reported to down-regulate miRNA-21 and up-regulated PTEN expression, therefore, enhances autophagy (Figure 4).200 Other ursolic acid derivatives, ilekudinol A (Pubchem CID: 10718549) and ilekudinol B (Pubchem CID: 10647480) were identified from *Weigela subessilis* (Caprifoliaceae) inhibits PTB1B and having IC50 29.1 and 5.3µM.201 Studies suggest anti-diabetic and anti-inflammatory properties of ursoic acid that need further targeted studies. Another good example of GRE binding triterpenoids is betulinic acid (Pubchem CID: 64971). Its mechanism was confirmed with help of *in vivo* administration of progesterone, actinomycin D and cycloheximide to block different target proteins activity.202 Logasin, morroniside, and ursoic acid isolated from the fruits of *Cormus officialis* Sieb. Zuc were reported to ameliorate T2DM and oxidative stress. A synergistic effect between logasin (Pubchem CID: 87691) and ursoic acid was also reported.203 Corosolic acid (Pubchem CID: 6918774), a
constituent of *Lagerstroemia speciosa* (Lythraceae) was reported to decrease blood sugar levels in human subjects within 60 min of administration. 1-Hydroxyurosesolic acid (corosolic acid) purified from the leaves of *L. speciosa* (Lythraceae) was a better inhibitor of α-glucosidase (IC50 3.53 µg/mL) than acarbose (IC50 1.82 µg/mL). It was reported to suppress IKKβ phosphorylation, and downregulate proinflammatory cytokines expression i.e. TNF-α, IL-6, and NF-κB along with iNOS, and COX-2. It was reported to improve the signal transduction through modification of IRS-1, AKT, LKB1 dependent AMPK activation. It was also shown to inhibit ERK1/2 and p38 MAPK phosphorylation, NADPH oxidase activity, ROS generation and NOX4, NOX2, p22 and p47 expression in cell lines treated with high glucose levels. These observations suggest the protective effects of corosolic acid in T2DM are mediated through inhibition of p38/MAPK, ERK1/2 pathways and activation of IRS-1/Akt pathway. Additionally, its ability to inhibit inflammation and oxidative stress makes it useful to treat T2DM. Further, corosolic acid was reported to regulate Drp1 phosphorylation in AMPK dependent manner and therefore block NOX2 oxidase and NLRP3 inflammasome activation in the endothelium that prevents mitochondrial fusion. Oral treatment with asiatic acid (Pubchem CID: 119034) (20 mg/kg body weight) increases the GLU-4 expression and Akt phosphorylation, which consequently improved the glucose levels, lipid peroxidation, and oxidative stress (Figure 4). Another study carried out on Wistar rats and GK rats, asiatic acid treatment decreased the insulin resistance indicated by decreased glucose (P < 0.01) and insulin (P < 0.05) levels. It was also found to reduce islet fibrosis in rats therefore, may play a role to improve islets dysfunction. Tormentic acid (Pubchem CID: 73193) was reported to ameliorate the insulin resistance in high-fat-fed C57BL/6J mice. It was also reported to reduce visceral fat mass and hepatic triacylglycerol contents and prevent degeneration of hepatocytes. Tormentic acid was reported to increase AMPK and Akt phosphorylation and GLUT4 translocation. Furthermore, it was reported to reduce PEPCK, G6 Pase, SREBP-1c and apo C-III genes expressions and increased PPAR-α expression. Therefore, it was suggested to be useful in hyperlipidemia and T2DM (Figure 4). Euscaphic acid (Pubchem CID: 471426) and p-coumarylurosesolic acids (Pubchem CID: 5315344) from *Sanguisorba tenuifolia* (Rosaceae) exhibit dose dependent α-glucosidase inhibitory activity and having IC50 values 0.67 and 0.62 mM, respectively, comparable with acarbose (IC50= 0.79 mM). Maslinic acid (PubChem CID: 73659) was reported to inhibit glycogen phosphorylase and therefore, increase glycogen content in HepG2 cells. It was reported to activate Akt specifically as activity of Akt could be blocked by wortmannin.

Figure 4: Schematic representation of proposed anti-diabetic mechanism of triperpenes
treatment. Moreover, it was shown to phosphorylate IRβ-subunit, and GSK3β, hence it decreases adiposity and insulin resistance, and increase hepatic glycogen contents in high-fat diet fed mice model.\textsuperscript{212}

**Lupanes:** Betulin (PubChem CID: 72326) was one first triterpene, isolated by Lowitz in 1788 from birch bark. Later on, it was reported from several species of Butulaceae family. Betulin was reported to decrease blood glucose level and inhibit α-glucosidase and SREBP activity when compared with acarbose.\textsuperscript{213} Betulinic acid (PubChem CID: 64971) was reported to significantly inhibit the hepatic glucose production and PGC-1α, PEPCK, and G6Pase gene expression. It activated AMPK and suppressed the CREB expression level. All these effects were abolished when cells treated with AMPK inhibitor indicated the AMPK-dependent inhibitory effect of betulinic acid on hepatic glucose production. Additionally, betulinic acid increased the CAMKK, AMPK and ACC phosphorylation, and suppressed hepatic glucose production. All these effects also abolished in presence of STO-609 (a CAMKK inhibitor). Results established that betulinic acid control T2DM through CAMKK-AMPK-CREB signaling pathway modulation (Figure 4).\textsuperscript{214,215} In silico lupane triterpenes, lupeol and betulinic acids act as allosteric inhibitors of PTP1B by targeting its less conserved hydrophobic allosteric site.\textsuperscript{216} Lupeol (PubChem CID: 259846) 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. It was also found to modulate AST, ALT, ALP; HK; G-6-PDase; G-6-Pase, F-1,6-BPase, LDH and pyruvate kinase activities in T2DM rats. Therefore, lupeol, increases the hepatic glucose utilization in T2DM rats by stimulating insulin secretion from β-cells along with antioxidant activities.\textsuperscript{214,217} Lupeol derivative, 2,3-seco-20(29)-lupene-2,3-dioic acid, isolated from *Fagus hayatae* (Fagaceae) leaves also reported to inhibit α-glucosidase, with I\textsubscript{50} 62.1 μM which was higher than acarbose.\textsuperscript{218} A new pentacyclic triterpenes 23,28-dihydroxylupan-20(29)-ene-3β-carboxylic acid, isolated from stem bark 80% ethanol extract of *Sorbus decora* C.K. Schneid reported to increase glucose uptake in C2C12 cells and showed anti diabetic activity.\textsuperscript{219}

**Hapone:** Hapone (PubChem CID: 10115) and lupine are sometime ambiguous terms and referred as steroidal terpenoids. 29-Nor-21α-H-hopane-3,22-dione, 21α-H-hop-22(29)-ene-3β, 30-diol and betulin were identified from *Salacia chinensis* stems and were reported to inhibit α-glucosidase and aldose reductase. These hapones were also found to have antioxidant potential.\textsuperscript{220} A hapone triterpene, 3β-hydroxy-21 (22)-hopen-30-oic-acid isolated from *Dipentodon sinicus* (Celastraceae), a plant known for the treatment of inflammation.\textsuperscript{221} Hapone-6α,22-diol was identified from the Antarctic lichen *L. carpathica*, and was reported to be a potent inhibitor of PTP1B with a I\textsubscript{50} value of 3.7 μmol/L. It showed selective inhibition of PTP1B over other PTPs.\textsuperscript{222} Ganoderic acid Df (PubChem CID: 57402147) purified from *Ganoderma lucidum* (Leyss. ex Fr.) Karst was reported to have I\textsubscript{50} 22.8 μM toward aldose reductase. Carboxyl group of side chain of Ganoderic acid Df was reported to be essential for inhibitory activity as its methyl ester had I\textsubscript{50} 200 μM. Ganoderic acid B (PubChem CID: 471003) was reported to have hepatoprotective activity and reduce GOT/GPT levels in the serum. Another hopane triterpene i.e. ganosporeric acid A (PubChem CID: 471002) decreased GPT activity after CCl4 and GaNI induced liver injury.\textsuperscript{223}

**Gammacerane:** This category of triterpenoids is less explored or present in some selected plants. Some of gammacerane triterpenoids like tetrahymanol (PubChem CID: 168951), ephakonanediol, ketohakonanol (PubChem CID: 101280264) and hakonanediol were isolated from *Adiantum monochlamys*.\textsuperscript{224} *Swertia chirayita*, a famous plant for its medicinal properties to treat liver disorders, malaria, diabetes, fever, and skin diseases was found to have gammacerane triterpenoid, kairenalen along with other compounds of medicinal importance. Another plant, *Ailanthus excelsa* reported for hypoglycemic effects in the STZ-induced diabetic rats in oral glucose tolerance test. Long duration administration of the plant produced a significant hypoglycemic effect. Plant was reported to contain gammacerane-3,21-dione (PubChem CID: 15767895).\textsuperscript{225} More selective studies of these compounds are required to explore their medicinal use.

**Tetracyclic triterpenes:** Tetracyclic triterpenes are less abundant in nature as compared to pentacyclic triterpenes. These are four ring structures and similar to sterols, except for the three methyl group substituents at the C-4, and C-14 positions. Triterpenoids can be divided into tetracyclic derivatives of dammarane, cucurbitane, euphane, protostane, lanostane, and cycloartenane.

**Dammarane:** Dammarane (PubChem CID: 9548714) derivatives are found to be distributed across the Araliaceae, Cucurbitaceae, Scrophulariaceae, and Rhamnaceae families of plant kingdom. *Gynostemma pentaphyllum* (Cucurbitaceae) yielded three compounds namely, 20S-dammarane-24(25)-ene-3β,20,21-tetrol, (20R,23R)-3β,20-dihydroxydammarane-24-ene-21-oic acid-21,23-lactone and 3β-hydroxyetio-17b-dammarane acid inhibits PTB1B with IC\textsubscript{50} 15.2, 8.4, and 13.1 μM respectively.\textsuperscript{226} Celastrol (PubChem CID: 122724) was reported to activate PGC-1α which activates heat shock factor 1 (HSF1) and increases energy expenditure. This action of celastrol is against obesity, insulin resistance, and hepatic steatosis due to increased mitochondrial functions. Celastrol was also reported to inhibit or reduce the production of NO synthase, COX-2 and CC chemokine ligand 2 and therefore, cytokine-induced cell death. Moreover, celastrol, inhibit NF-κB activation and therefore pro-inflammatory cytokines (Figure 4).\textsuperscript{227} Pentacyclic triterpenoid from *Aristolba rivularis* were reported to increase basal and insulin-stimulated glucose uptake, GLUT4 translocation, and IRS-1, Akt, and Erk1/2 phosphorylation.\textsuperscript{228} Platycodin D (PubChem CID: 162859) from *Platycodi Radix* significantly decreased the serum levels of glucose, insulin, IL-6, IL-1β, TNF-α, and IL-17A and increased IL-10 level. It effectively down-regulated liver AST, ALT, TC,
and TG and attenuated histological change. Results have shown that it exerts beneficial effects through inhibition of the JAK and STAT-3 phosphorylation and increasing the expression of Foxo3. Triterpenoid glycoside and senegin II (Pubchem CID: 11953920) isolated from root of Senega radix Linn. showed hypoglycaemic activity. Triterpenoid glycoside desmethoxysenegen II isolated from the rhizomes of Polygonum senega Linn. (N.O. Polygonaceae) reported to reduce blood glucose of healthy mice and significantly decrease glucose level in KK-Ay mice.

**Cucurbitane:** The natural cucurbitacins were identified from Momordica charantia L. (Cucurbitaceae). Hence, the name of cucurbitane (PubChem CID: 71306378) derived from the bitter melon having bitter principles, the fruit of M. charantia. Triterpenoids have been reported to have permeability problem and hence, are less absorbed through the intestine. In contrast, cucurbitane isolated from M. charantia i.e. 3-β,7-β,25-trihydroxycucurbita-5,23(E)-dien-19-al (PubChem CID: 4477792) and momordicines I (PubChem CID: 101293615) and II were reported to have good permeability coefficient values to the basolateral side at 9.02 × 10⁻⁶, 8.12 × 10⁻⁶ and 1.68 × 10⁻⁶ cm/s, respectively. Most of the compounds identified from the M. charantia fruits have been tested for their anti-diabetic efficacy being the use of this fruit as anti-diabetic traditional medicine. A number of triterpenoids have been isolated and characterized from the plant and the plant has been shown to have efficacy to treat diabetic humans and animal models, it is difficult to name the compound responsible for its anti-diabetic activity.

**Euphane:** A very small number of eupahne triterpenes have been reported from the natural sources. Tetracyclic triterpenoid, euphan-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 corticosterone, 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 (Figure 4). Bark extracts of Boswellia serrata was reported to contain 20, 24 dihydroxyeupha-2, 8, 22-tiene shown anti-inflammatory activity.

**Protostane:** Protostanes are the stereoisomer of dammarane type triterpene, with structural rearrangement in 8a-CH3, 9β-H, 13α-H, and 14β-CH3 positions. These triterpenes are found in the plants of the Alismataceae family. Alisol A (PubChem CID: 15558616), alisol B (PubChem CID: 189051), alisol A 24-acetate and alisol B 23-acetate identified from Alismatis Rhizoma were found to be effectively delaying the cholesterol effects. Diet having even 0.1% nay of these compounds reduce the cholesterol levels by more than 50%. Alisol B was found to be most effective and reduced cholesterol levels by 61%. These compounds also found to effectively protect the liver damage, induced by D-galactosamine and CCL4 in mice liver. Another prostate, alisol F (PubChem CID: 76310822) was reported to inhibit α-glucosidase in a dose-dependent manner (0.125–2.5 mM). *Alisma orientalis* is another plant of the same family and contains protostanes, which is well-known to treat T2DM. Alisol M 23-acetate and alisol A 23-acetate from *A. orientalis* were reported to modulate farnesoid X receptor (FXR) as well as GAL4, SHP, CYP7A1, and PLTP promoters in dose-dependent manner, just like chenodeoxycholic acid (CDCA). Study concluded that alisol M 23-acetate and alisol A 23-acetate exerts anti-T2DM effect through FXR pathway. FXR downregulated the expression of PEPCK and G-6-pase to decrease the blood glucose levels.

**Lanostane:** Lanostanes are less frequently observed in the plant kingdom. Mostly this class of compounds was characterized by the *trans* ring junction of the A/B, C/D rings and reported from sponges and fungi. Most the terpenes of this category were reported for their anti-proliferative activity. However, Ganoderic acid A (PubChem CID: 471002), Ganoderic acid H (PubChem CID: 471005), lucidenic acid B (PubChem CID: 102410351) from *Ganoderma lucidum* and alisol F (PubChem CID: 189051), lucidenic acid B (PubChem CID: 102410351) from *Ganoderma lucidum* were reported for their anti-inflammatory and anti-ageing activity through inhibition of NF-κB in mice. It has been reported to improve the insulin sensitivity through regulation of SREBP pathway (Figure 4). Butyl ganoderate A (PubChem CID: 46881265), butyl ganoderate B (PubChem CID: 46184562), butyl lucidenate N (PubChem CID: 46184563), and butyl lucidenate A (PubChem CID: 46184564) were reported for inhibitory effects on adipogenesis in 3T3-L1 cells through down-regulation of SREBP-1c. *Poria cocos*, known as Bai Fu Ling in Chinese, was reported to contain lanostane-type triterpene, dehydrotraminetolic acid and dehydrotramanolacic acid, found to be effective in hyperglycemia at dose of 110 mg/kg body weight/day. Crude extract of *P. cocos* was also reported to reduce blood glucose level by enhancing insulin sensitivity through AMP-activated protein kinase. Two lanostane triterpenes (hydroxylanosta-9,24-dien-21-oic acid, and methyl-hydroxylanosta-9,24-dien-21-oate) isolated from stem bark of *Protorhus longifolia* (Benrh) Engl were reported to inhibit lipid digestive enzymes (pancreatic lipase, cholesterol esterase) and HSL activities with IC50 values ranging from 60.1 to 677.8 µM. These compounds also reported to stimulated glucose uptake in both 3T3-L1 and C2C12 cells anti-
inflammatory activity. Ganoleucins M, N, P identified from the fruiting bodies of *Ganoderma leucocontextum*, were reported to be potent inhibitor of α-glucosidase with IC₅₀ values of 13.6, 2.5, and 5.9 µM, respectively. 240

**Cycloartane:** Cycloartanes or 19-cycloartenanes are group of major components in Leguminosae (Fabaceae, Aesculus hippocastanum, astragalus), Passifloraceae (*Passiflora edulis*) and Ranunculaceae (*Cimicifuga racemosa*). Cycloartenol (PubChem CID: 160497) 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. *Aloe barbadensis* MILLER and *Aloe arborescens* MILLER var. natans LENS (Liliaceae) were reported to contain lophenol (PubChem CID: 1604827), 24-methyl-lophenol (PubChem CID: 52836407), 24-ethyllophenol (PubChem CID: 101614269), cycloartenol (PubChem CID: 12760132), and 24-methylene-cycloartenol (PubChem CID: 9547213). These phytosterols significantly decreased the HbA1c levels by 15 to 18% in T2DM mice. These phytosterols were also reported to decrease fasting blood glucose levels by 64%, 28%, 47%, 51%, and 55% respectively after 28 day treatment. 241 Other cycloartanes, i.e. mangiferonic acid (PubChem CID: 14034474), mangiferolic acid (PubChem CID: 45270099), ambonic acid (PubChem CID: 101286242), and ambolic acid (PubChem CID: 101286241) were reported to α-glucosidase inhibitory activities (IC₅₀= 31.2 to 112 µM). 242

*Ganoderma resinaceum* Boud. (Polyporeaeae) yielded ganoderesin B (PubChem CID: 102526029), ganoderol B (PubChem CID:13934286) and lucidone A (PubChem CID: 71453988), showed inhibitory affects against the increase of ALT and AST levels in HepG2 cells induced by H₂O₂ and showed the hepato-protective activities. 243 Cimyunmins A–C, characterized from the fruit of *Cimicifuga yunnanensis* exhibited sunitinib comparable anti-angiogenic activities through directly targeting VEGFR2-signaling pathways. 244

Pistagreemic acid from *Pistacia chinesis* var. integerrima (Anacardiaceae) was reported to inhibit the rat intestinal α-glucosidase (IC₅₀=62.47 µM, acarbose IC₅₀= 38.92 µM). 245

**Other terpenes:** *G. lucidum* containing antcin H (PubChem CID: 44424393), dehydroabietonic acid, eburicoic acid (PubChem CID: 73402), methyl antcinate B (PubChem CID: 53319129) and dehydroabietic acid (PubChem CID: 15250826) regulate the 3T3-L1 adipocytes differentiation and the gene expression of adiponectin through inhibition of Cox-2, Twist1, IGF-1R, Stat3, and Src. 246,247 Dehydroabietic acid administration to STZ-diabetic mice was reported to increase the GLUT4 expression and AMPK phosphorylation and decrease the PEPCK and G6Pase mRNA levels. It was also reported to increase the expression levels of PPARα and CPT-1a and decrease FAS and SREBP2 expression, which indicated its efficacy in metabolic disease T2DM and hyperlipidemia (Figure 4). Oral administration (100 mg/kg body weight) of methyl-3β-hydroxylanosta-9,24-dien-21-oate, a lanosterol triterpene from *Protorhus longifolia* for 14 days in the diabetic rats reduced blood glucose levels by 37% and improved glucose tolerance. Treatment increased the hepatic glycogen content, HK and GK activities and decreased G-6-Pase activity. It also increased the activities of SOD and CAT and decreased the MDA contents that improved anti-oxidant status and therefore, controlled the postprandial hyperglycemia. 248 Punicic acid from *Punica granatum* Linn, prevent T2DM by inhibiting or activating certain transcriptional factors, such as NF-kB and PPAR-γ and decrease the fasting blood glucose levels significantly. 249 Triterpenic acid from *Prunella vulgaris* L administration for six weeks significantly decreased the body weight and BG, FMN, MDA, NO levels and NOS activity in serum. It was also reported to increase the SOD mRNA expression in pancreatic β cells. 250 Sesquiterpene lactones (PubChem CID: 338659) isolated from *Lactuca indica* Linn. moderately decreased plasma glucose in STZ induced diabetic rats. 251 Glucosol (PubChem CID: 6918774) isolated from *Lagerstroemia speciosa* Linn. leaves showed significant glucose transport-stimulating activity at a concentration of 1 µM and significantly reduced blood glucose levels. 252 Sesquiterpene 3-hydroxycaecalolide isolated from *Psacalium decompositum* (A. Gray) H. Rob. & Brettell showed antihyperglycemic activity. 253 Palbinone (PubChem CID: 9841735), a triterpenes isolated from *Paeonia suffruticosa* Andrews showed increased glucose uptake and enhanced glycogen synthesis by activating AMPK in insulin-resistant human HepG₂ cells. 254 Limonoids: Azadiradione (PubChem CID: 5000606) and gedunin (PubChem CID: 3458), limonoids from *Azadirachta indica* reduced post-prandial hyperglycemia by inhibiting HPA (anti-diabetic target) with IC₅₀ value of 74.17 and 68.38 µM, respectively. 255 Abietic acid (PubChem CID: 10569), dehydroabietic acid (PubChem CID: 1201531) and squalene (PubChem CID: 638072) from *Abies balsamea* (L.) Mill. were reported to decrease the G6Pase activity and stimulate glycogen synthase. These effects involved Akt, AMPK and GSK-3 phosphorylation. 256 11-Ketoβ-boswellic acids were reported to prevent insulinitis, and hyperglycemia. These acids were reported to significantly reduce pro-and anti-inflammatory cytokines and blood glucose. 257 Abietane-type diterpenoids, danshenols A and B isolated from roots and rhizome of *Salvia miltiorrhiza* Bunge showed inhibitory activity against rat lens. 258 Hook. F. & Thomson reported that Tinosporas isolate isolated from ethanolic extract of *Tinospora cordifolia* (Willd.) tends to have anti-hyperglycemic activity 28.8% (P <0.01) in STZ model as compared to metformin 20.6% (P<0.05). 259 Limonoids from *Swietenia humilis*, 2-hydroxy-testigloyl-6-deoxyswietenine acetate, humulin B, methyl-2-hydroxy-3-β-tigloyloxyl-1-oxomeliac-8(30)-enate were found to decrease the glycemia and increase hepatic glycogen contents in STZ-induced T2DM rats. 260 Catalpol isolated from *Rehnmannia glutinosa* roots has been reported to act on AMPK/NOX4/P3K/AKT pathway thereby exhibiting anti-diabetic effects in vivo and in vitro. 261 Dehydroabieoric acid from *Antrodia camphorata* was reported to markedly decrease blood glucose (42.6–46.5%), TG (P < 0.001) and TC (P < 0.01) levels. It was reported to increase the expression levels of GLUT4, PPARα, CPT-1a and AMPK phosphorylation in liver and skeletal muscle. It was reported to decrease mRNA levels of FAS, SREBP2, PEPCK and G6 Pase.
Hence, it was reported to be useful in diabetes as well as dyslipidemia.262

**SAPONINS**

Saponins are glycosylated compounds, widely distributed in the plant kingdom and traditionally, subdivided into triterpenoid, steroid glycosides, saponins, and furostanol saponins. Further, on the basis of their carbon skeletal these can be divided into 11 main classes: dammaranes, iridocaranes, lupanes, hopanes, oleananes, taraxasteranes, ursanes, cycloartanes, lanostanes, cucurbitanes, and steroids. Out of these, ursanes and oleananes are the major triterpenes in plants. A number of saponins were reported to stimulate the release of insulin and blocks the formation of glucose in the bloodstream. Examples of saponins included gingenoside, diosgenin, sassapogenin, sassapogenin, solasodine, quillaia, asteragaloide I, betulinic acid, elatinirnde, ginsenoside, glycyrhizic acid, ilesapoxin A1, jujubosides, notoginsenoside R1, saikosaponin, β-sitosterol etc.

**Dammarene:** The dammaranes are tetracyclic triterpenoids and can be divided into three subtypes with respect to their aglycone moiety, i.e. protopanaxadiol (PubChem CID: 3800204), propanaxtriol (PubChem CID: 22392424) and ocatillol (PubChem CID: 102058355). Protopanaxadiol-type ginsenosides (PGD) and its intestinal metabolite compound K from *Panax ginseng* decreased the expression of glucose-regulated genes, PEPCK and G6Pase in the treated groups. Protopanaxadiol and propanaxtriol ginsenosides isolated from *P. ginseng* were reported to decrease the TC and TG while increasing the HDL levels. It also significantly decreased MDA values of 0.17 μM equivalent to phlorizin (0.21 μM). Another dammarane saponin, dammarane-24-ene-21-oic acid-21,23-lactone was reported to inhibit PTP1B activity. Damulin A, and damulin B identified from *G. pentaphyllum* were reported to activate AMPK in L6 myotube cells. Hence, these compounds increased β-oxidation and GLUT4 translocation (Figure 5). Treatment of rat pancreatic islets with 500 μM phanoside, a compound identified from *G. pentaphyllum* increase the insulin release by 10-fold at 3.3 mM glucose and almost 4-fold at 16.7 mM glucose. In the same experiment, treatment of islets with 2 μM glibenclamide increased the insulin by 2-fold. Other dammaranes from *G. pentaphyllum* were reported to have potent insulin releasing activity at both initiatory and potentiatory concentration of glucose in rat pancreatic islets. 3β-Acetoxy-20-oxo-21-nordammaran-23-oic acid has been reported to inhibit α-glucosidase. 20S,23S-3β,20-Dihydroxydammarane-24-ene-21-oxo aciden-21,23-lactone and (20R,23R)-3β,20-dihydroxydammarane-24-ene-21-oxo acid 21,23-lactone were reported to inhibit PTP1B activity. Damulin A, and damulin B identified from *G. pentaphyllum* were reported to decrease glycogen content in normal and diabetic livers. Gymnema sylvestre (Retz.) Schult contains 3-O-β-D-glucuronopyranosyl-21-0-methylbutyryl-22-O-2-tigloyl gymnemannin saponin and showed inhibitory activity on sodium-dependent glucose transporter 1 (SGLT1) with low IC_{50} values of 0.17 μM equivalent to phlorizin (0.21 μM). Another saponin dihydroxy gymnemic triacetate isolated from aceton extract of the same plant reported to have hypoglycemic and hypolipidemic activities. It promotes islet-β-cells regeneration and insulin secretion. It was also reported to increase peripheral blood glucose utilization and prevent the intestinal sugar absorption. Also, *G. sylvestre* R. alcoholic leaves extract was reported to decrease glycojen content in normal and hyperglycemic rats. Gymnemic acid V (PubChem CID: 14683206) identified from *G. sylvestre* was reported to increase endogenous insulin release, promote regeneration of islet cells and glucose absorption from intestine. It was also reported to increases glucose utilization by increasing the activities of glucose utilizing enzymes, phosphorylase and decreasing the activities of glucoseoneogenic enzymes and sorbitol dehydrogenase.269 3-0[β-d-Xylopyranosyl-(1→4)-β-d-glucopyranosyl-(1→2)-β-d-glucopyranosyl-(1→4)-α-l-arabinopyranosyl]-16α-hydroxy-13β, 28-epoxy-olean-30-al identified from *Primula denticulate* Sm. (Primulaceae) was reported to decrease the blood-glucose level significantly in the T2DM rat model. It was
found to be effectively restored the insulin level up to 31.49 µU/ml as compared with disease control (18.45 µU/ml). Schekwangsiensides A-G isolated from Schefflera kwangsiensis were reported to have moderate hepatoprotective activities. Adonitol esters, scorzonerosides A, B, and C isolated from the roots of Bupleurum scorzonerifolium were reported to have hepatoprotective activities in the mice.

Cycloartane: Cycloartane-type saponins were reported to decrease the blood glucose and HbA1C levels, and increases plasma insulin levels. A cycloartane glycoside isolated from the Cimicifuga foetida rhizome exhibited anti-complement activity having IC50 value of 29.6 μM. This type of compounds can be used to prevent secondary complications of T2DM. A new cycloartane triterpene, 23-oxo-3α-hydroxy-cycloart-24-en-26-oic acid was reported to strongly enhanced adipogenesis in 3T3-L1 cells with an EC50 of 7.7 μM. It is responsible for two thirds of the activity of the active fraction of Larix laricina. Another compound from L. laricina, 13-epitorulosol also potentiated adipogenesis (EC50=8.2 μM). The plant Krameria pauciflora MOC et. Sesse ex DC. showed anti-inflammatory effect similar to indomethacin (10 mg/kg) when the methanol and dichloromethane extracts, which contain a cycloartane-type triterpene and an sterol, were administered orally in diabetic rats. Compounds also exhibited anti-hyperglycaemic effects. Astragaloside IV (AGS-IV) isolated from the root of Astragalus membranaceus (Fisch.) Bunge, was reported as ROS scavenger and aldose-reductase inhibitor. Astragaloside IV (AGS-IV) reduced sciatic motor nerve conduction velocity in STZ induced T2DM rats. It was found to reduce blood glucose and HbA1C levels, and increase plasma insulin levels. AGS-IV increased glutathione peroxidase and Na+ K+-ATPase activity in the nerves and erythrocytes of T2DM rats, hence it protect the progression of peripheral neuropathy in STZ-induced T2DM rats.

Lanostanes: Lanostane (PubChem CID: 9548665) has been reported as insulin sensitizer through the activation of PPAR and RXR receptors. Lanostane-type triterpenoids, inotolactones A and B isolated from the submerged culture of chaga mushroom, Inonotus obliquus bearing α,β-dimethyl, α,β-unsaturated δ-lactone side chains, exhibited potent alpha-glucosidase inhibitory activities than the positive control acarbose. Two lanostane triterpenes, 3β-hydroxylanosta-9,24-dien-21-oic acid and methyl-3β-hydroxylanosta-9,24-dien-21-oate isolated from the stem bark of Prototous longifolia stimulated glucose uptake in C2C12 muscle cells and 3T3-L1 adipocytes. 3β-Hydroxylanosta-9,24-dien-21-oic acid also significantly reduced triglyceride accumulation in mature differentiated 3T3-L1 adipocytes.

Cucurbitane: Cucurbitane (PubChem CID: 71306378) saponins are the compounds isolated mainly from Cucurbitaceae family and named after it. Major plant species is Momordica charantia, well known anti-T2DM plant in traditional medicines. Structures and biological activities of cucurbuitanes have been well reported. Cucurbitane can be divided in 12 categories and are shown to have strong efficacy in T2DM (EC50= 1nM and maximum: 10–100nM) equivalent to insulin (100nM). This efficacy was reported to be achieved through increased GLUT4 translocation and phosphorylation of AMPK (T172) and acetyl-CoA carboxylase (S79), analogue of well-known AMPK activator AICAR. A cucurbitane-type triterpenoid [(19R,23E)-5β, 19-epoxy-19-methoxy-cucurbita-6,23,25-trien-3 β-o-l] and charantin were reported to up-regulate the IR, IRS and other proteins of insulin signaling pathway, just like metformin in the alloxan induced T2DM rats. Resultatn

Figure 5: Schematic representation of proposed anti-diabetic mechanism of saponins
reduction in blood glucose (31.48.6%) and lipids (13.5-42.8%) and an improved glucose tolerance was noticed in T2DM rats.\(^{280}\) Momordicicosides Q, R, S, T, and karavilioside XI exhibited a number of biologic effects beneficial to diabetes and obesity in L6 myotubes and 3T3-L1 adipocytes through increased GLUT4 translocation to the cell membrane and AMPK activity (Figure 4). These saponins were also reported to increase fatty acid oxidation and glucose disposal in insulin-sensitive as well as in insulin-resistant mice.\(^{281}\) 19-Nor-cucurbita-5(10),6,8,22-(E),24-penta-3β,ol, and karavilagenin E showed acute hypoglycemic effect that was abolished by GLP-1 receptor antagonist exendin-9. It supports the fact that these cucurbitanes stimulates GLP-1 secretion in addition to GLU-4 translocation and AMPK activation.\(^{233}\) Mogroside V (PubChem CID: 102004427) and its aglycone mogrol from Siraitia grosvenorii were reported to be potent activators of AMPK (EC\(_{50}\) 20.4 and 4.2 μM).\(^{282}\) Echinocystis fabacea from the same family contains isoecurbitacin B was reported to have a hepatoprotective effect in rats with experimental cholestasis.\(^{283}\)

**Lupanes:** Lupane (PubChem CID: 3083568) has been reported to have anti-oxidant, anti-hyperlipidemic and anti-diabetic activities. Compound in this class of saponins were reported to decrease the MDA levels, increase the GSH levels and the activity of SOD and CAT significantly in the liver of T2DM rats.\(^{284}\) Lupane triterpenes are also reported to allosterically inhibits PTP1B. 2,3-seco-20(29)-Lupene-2,3-dioic acid has been reported to be the inhibitor of α-glucosidase type IV, with IC\(_{50}\) of 62.1 μM. The isolation of these compounds has never been reported. Recently, lupan triterpenes from *Aegle marmelos* namely; 20(29)-lupene-3α-ol (3) and 20(29)-lupene-3-on (4) were isolated from petroleum ether and chloroform crude extracts of the stem bark.\(^{284}\) The lupane-type triterpene, bacosine, obtained from the herb of *Bacopa monnieri* (Scrophulariaceae) also displayed antioxidant properties. This compound significantly decreased the level of malondialdehyde, increased the level of glutathione (GSH) and the activity of superoxide dismutase (SOD) and catalase (CAT) in the liver of diabetic rats.\(^{285}\)

**Tirucallanes:** Tirucallane (PubChem CID: 12312922) saponins are metabolically altered triterpenes and contain (13S,14R,17S,20S)-lanostane skeleton. Tirucallane-type triterpenoids have unique structures and various biological activities. A number of tirucallanes saponins have been reported from various plants, including niloticin, dihydroniloticin, piscidinol A, bourjotinolone A, 3-episapelin A, melianone, and hispidone. Most of tirucallanes exhibited cytotoxicity, hence were evaluated for anti-cancer activities. However, a very few tirucallanes have been reported for their antidiabetic activities. Till date only paramignyosides C, isolated from the water fraction of the *Paramignya scandens* stem and leaves, exhibited anti-inflammatory activities due to selective and potent inhibitory effect (IC\(_{50}\) 5.030.19 μM) on the production of IL-12 and p40 comparable to that of the positive control, SB203580 (IC50 5.000.16 μM).\(^{286}\)

**Hopanes:** Hopanes (PubChem CID: 10115) are the glycosylated triterpenoids same as lupane with hydroxyl group. 6α,22-Dihydroxyhopane and 15α,22-dihydroxyhopane has been reported from *Aegle marmelos*.\(^{287}\) Hopane-6α,22-diol from *Lecidella carpathica* (Lecanoraceae) has been reported to inhibit PTP1B with an IC\(_{50}\) value of 3.7 μmol/L.\(^{282}\) Hopane was reported to be present abundantly in *Salacia* roots and reported to treat T2DM, obesity, hyperlipidemia and cardiovascular complications. It was found to modulate PPARα, angiotensin II type 1 receptors, α-glucosidase, aldose reductase and pancreatic lipase.\(^{288}\) Salacinol isolated from the *S. chinensis* was reported to be α-glucosidase inhibitor.\(^{289}\)

**Oleananes:** Oleanane (PubChem CID: 9548717) saponins are the glucosides of oleanolic acid and ursolic acid, widely existing in nature. These can be classified as monodesmosides due to glycosylation at C-3 or C-28, and bisdesmosides due to glycosylation at both C-3 and C-28. Activity of these saponins is believed to be dependents on their ring substations. It was reported that 2′-O-β-D-glucopyranosyl moiety of the glucuronic acid reduced the postprandial absorption of food whereas the 28-ester glucose moiety markedly reduced it with a result to improve in blood glucose levels. Hence, 3-O-glycosides moieties was reported to be essential for the activity.\(^{290}\) It was shown that the 3-O-glycoside moiety is essential in oleanolic acid glycosides from the root of *Aralia elata*, for hypoglycemic activity. Moreover, it was observed that 4′-O-arabinofuranosyl showed better activity than 3′-O-glucopyranosyl moiety.\(^{291}\)

The oleanane-type saponins from *Gymnema alternifolium* were reported to have an anti-sweet activity. Oleanane type triterpene glycosides from *Helianthus annuus* was also reported to have significant anti-inflammatory activity in the range 65-262 mmol. The oleanane saponins from *Terminalia arjuna* were reported to have great potential in free radical scavenging and therefore, these are cardioprotective and anti-T2DM. Four oleanane-type triterpenes were isolated from an EtOAc-soluble extract of fruit peels of *Camellia japonica* (Theaceae), and showed strong PTP1B inhibitory activity (IC\(_{50}\) values ranging from 3.7±0.11 to 6.40±0.81 μM) and cytotoxicity (IC\(_{50}\) values ranging from 0.51±0.05 to 13.55±1.44 μM). Oleane triterpenes and O-caffeyl quinic acid enriched *Viscum schimperi* Engl. showed the potential antidiabetic activity in streptozotocin-induced diabetic rats at two dose levels.\(^{292,293}\) Oleane-type triterpenoid saponin isolated from the *Momordica cymbalaria* Fenzl (Cucurbitaceae) fruit powder was found to be useful in diabetic peripheral neuropathy (DPN) in Male Wistar rats diabetic model. It reduced AR and SDH activities and sorbitol accumulation significantly. It also improved muscular grip strength, reaction time to pain sensation and nerve conduction velocity. Hence, it may be useful to manage and treat diabetic neuropathy.\(^{294}\) Oleaneolic acid and hederagenin (10 μM) from the roots of *Gypsophila oldhamiana* (Caryophyllaceae) have shown 73.07% of GP inhibition, as compared to gypsogenin, with 45.11% inhibition. The activity was reported to be dependent on the hydroxyl group at C-3 and CH\(_3\) or CH\(_{2}\)OH groups at C-23 in the oleanane skeleton.\(^{295}\) 2α,3β,21β,22α,29α-Pentahydroxyolean-12-en-28-oic acid from *Oriagnum majorana* leaves extract was reported to be excellent anti-glycation agent having activity near to the...
standard aminoguanidine. *Celastrus vulcanicola* (Celastraceae) contains 7β-hydroxy-3-oxo-5A-friedoolean-28-oic acid was reported to increase the IR phosphorylation.296

Palustrosides I (PubChem CID: 10373131), II (PubChem CID: 100918547) and III (PubChem CID: 100918548) isolated from *Lathyrus palustris* were reported to have hepatoprotective effects in immunologically injured in rat hepatocytes. The 2α,3α,19α,24-tetrahydroxyolean-12-en-28-oic acid 28-O-β-D-glucopyranosyl ester, 2α,3α,19α,23-tetrahydroxyolean-12-en-28-oic acid 28-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl ester and 2α,3α,19α-trihydroxyolean-12-en-28-oic acid 28-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl ester isolated from the leaves of *Callicarpa nudiflora* Hook showed pronounced activity against in D-galactosamine-induced toxicity in WB-F-344 rat hepatic epithelial stem-like cells. A new saponin elatosides E (PubChem CID: 3083469) isolated from roots of *Aralia elata* seems to have potent hypoglycaemic activity in oral glucose tolerance test in rats. Hypoglycemic mechanism may be due to inhibition of hepatic gluconeogenesis or glycogenolysis.299 Schrad reported inhibiting glucose activity and ethanol absorption of Momordin Ic (PubChem CID: 176596), isolated from methanolic extract of *Kochia scoparia* (L.) in rats.271 Momordin Ic and oleanolic acid 3-O-glucuronide for their cytotoxicity, hence studied for their anti-cancer activities. These reported to inhibit PI3K-Akt and MAPK pathways, hence control the blood glucose levels.304 The α,β-unsaturated ketone, 3β,21α-28α,6,23-trienolide, isolated from acetone extract of *Anemarrhena asphodeloides* was reported to possess good anti-oxidant potential and have inhibiting effect on α-glucosidase inhibitory activity with IC50 value of 1.71 µg/mL.305 Hederagenin, 30-norhederagenin yemuoside from *M. charantia* showed strong α-glucosidase inhibitory activity with IC50 value of 48.0, 42.7, 39.6 and 49.1 µM, respectively.306 Bioassay-guided revealed rhododendric acid A, as an inhibitor of PTP1B from *Rhododendron brachycarpum* G. Don (Ericaceae).307

**Steroids:** Rg5 (PubChem CID: 11550001) and compound k, steroidal saponins identified from black ginseng were reported to effectively control hyperglycemia and β-cell function by suppressing NF-κB and G-6-Pase even at the non-stimulatory glucose concentrations. Its capability to regenerate beta cells and anti-oxidant activity were reported as the reason to release of insulin. A novel steroid 28-Nor-22(R) Witha 6,23-trienolide, isolated from acetone extract of *Elephantopus scaber* (Linn.), reported to have significant anti-diabetic activity by reducing the elevated blood glucose levels and restoring the insulin levels in STZ induced diabetic rats. Hypoglycemic and anti-diabetic activity is due to stimulating effect on insulin release though inhibition of G-6-Pase even at the non-stimulatory glucose concentrations. Its capability to regenerate beta cells and anti-oxidant activity were reported as the reason to release of insulin. A novel steroid 28-Nor-22(R) Witha 6,23-trienolide, isolated from acetone extract of *Elephantopus scaber* (Linn.), reported to have significant anti-diabetic activity by reducing the elevated blood glucose levels and restoring the insulin levels in STZ induced diabetic rats. Hypoglycemic and anti-diabetic activity is due to stimulating effect on insulin release from beta cells of the pancreas or due to increased cellularity of the islet tissues and regeneration of granules in the beta cells.312

Other triterpenoid saponins: Ginsenosides Rd and R-Rh2 were shown to improve insulin signaling and inhibit apoptosis; therefore, these terpenes were indicated to have therapeutic potential to control T2DM and T2DM-induced neurodegeneration.313 Chikusetsu saponin IVa (CHS) (PubChem CID: 3080813) from *Aralia taibaiensis* was reported to increase...
the insulin levels and decrease glucose levels dose dependently. It increases the intracellular calcium levels in βTC3 cells and phosphorylates PCK, hence increases insulin secretion. It also activates AMPK in normal as well as insulin resistant cells, therefore, increases glucose uptake and fatty acid oxidation and recommended to use both hyperlipidemia and T2DM.\textsuperscript{314} Centella asiatica was reported to yield asiaticoside, which modulate the PI3K/AKT/NF-κB, hence modulating inflammatory events induced in T2DM.\textsuperscript{315} Isopimarane and 11-deoxydiaporthenin A, characterized from the culture of Epicoccum sp. were found to be inhibitors of α-glucosidase with IC\textsubscript{50} values of 4.6±0.1 and 11.9± 0.4 μM, respectively.\textsuperscript{316} Dehydroabietic acid was reported to decrease plasma glucose, insulin, plasma TG and hepatic TG levels. It was also found to suppress MCP-1 and TNF-α and increased that of adiponectin in diabetic KK-Ay mice. Hence, it was effective in T2DM, hyperlipidemia and inflammation (Figure 5).\textsuperscript{317} Isotanshinone IIA (PubChem CID: 626354), dihydroisotanshinone I (PubChem CID: 89406), and isocryptotanshinone were reported to be non-competitive inhibitors of PTP1B, an important target of T2DM.\textsuperscript{318} Andrographolide 1 and 2, isolated from Andrographis paniculata (burm. f.) Nees (Acanthaceae) were reported to inhibit PTP1B an important protein in T2DM.\textsuperscript{319} Amotinflavone (PubChem CID: 5281600), a biflavonoid from Selaginella tamariscina and (-)-hyrtiosal a sesterterpenoid from the Hyrtios erectus were reported to be effective to treat diabetes nephropathy induced renal failure within 28 days. A dose of 90 μg/ml andrographolides also decreased the serum creatinine (54.73%), serum urea (63.92%) and urinary proteins (32.35%). Salvin, salvinic salvipholin and stevioside from Salvia miltiorrhiza were reported to maintain insulin homeostasis in insulin deficient animals, ameliorate diabetic nephropathy and improved beta cell health.\textsuperscript{319} Amentoflavone (PubChem CID: 5281600), a biflavonoid from Selaginella tamariscina and (-)-hyrtiosal a sesterterpenoid from the Hyrtios erectus has been reported to inhibit PTP1B an important protein in T2DM.\textsuperscript{320} Tanshinones (PubChem CID: 114917) isolated from Salvia miltiorrhiza Bunge, reported to have cardioprotective effects and anti-inflammatory activity was also reported to ameliorate renal hypertrophy and reduced the AGEs, angiotensin II (Ang II) (PubChem CID: 172198), TGF-β1, collagen IV, and monocyte/macrophage (ED-1). Tanshinone IIA (PubChem CID: 164676) was reported to have anti diabetic activity through modulation of PI3K/Akt-dependent pathway.\textsuperscript{321,322} Diterpenes (ginkgolide A, B, C, J and M) and sesquiterpene bilobalida from Ginkgo biloba were reported to increase catalase and decrease MDA in T2DM rats. It was also reported to upregulate IRS, GLUT-4, PPAR-α and downregulate PEPCK and TNF-α expression (Figure 5). Therefore, G. biloba was reported to modulate expression of key genes, involved in glucose homeostasis and effective in diabetes.\textsuperscript{323} Dolabellane diterpenes i.e. nigellamines (A3, A4, A5, and C), isolated from Nigella sativa, a common spice and food product in India were reported to promote the triglyceride metabolism through activating the PPAR-α that also controls the hyperglycemic conditions.\textsuperscript{324} Kaurane-type diterpen rebaudioside A, isolated from Stevia rebaudiana Bertoni, stimulates glucose-dependent manner (3.3 to 16.7 mmol/L), while insulin secretion depends on extracellular calcium. On the contrary, even the chronic consumption of 1000 mg rebaudioside A didn’t show any effect on T2DM.\textsuperscript{325} Isosteviol, another compound of same, class was reported to enhance peripheral glucose utilization and reduce palmitate induced β-cell through, increasing the expression of liver PPAR-α mRNA.\textsuperscript{326} Kaurenoic acid, a bioactive diterpene, from Wedelia paludosa was reported to be responsible for the hypoglycemic activity.\textsuperscript{326} However, reports are there to limit its use in T2DM. Forskolin (PubChem CID: 47936) was characterized from Coleus forskohlii was well reported to increase cAMP levels through adenylylate cyclase activation. It was found that administration of forskolin decrease the fasting glucose levels and oxidative stress due to macrophages inhibition.\textsuperscript{327} Carnosic acid (PubChem CID: 65126) and carnosol (PubChem CID: 2579) compounds of the labiate herbs were reported to be the activators of PPAR-α, a major clinical target for treatment of T2DM.\textsuperscript{328} Tinospora cordifolia, an important traditional medicinal plant was reported to be useful in hyperglycemic conditions in dose and time dependent manner. Some studies indicate the equal efficacy of T. cordifolia with the glibenclamide in alloxan induced T2DM rats.\textsuperscript{15,329} Plant was reported to contain a number of diterpenes and their glycosides i.e columnis, tinosporins, clerodane-type furanoditerpenes and nortriterpenes (cardifolisides A-C). However, individual compound(s) responsible for this activity couldn’t be identified till date.

**POLYSACCHARIDES**

Polysaccharides are most abundant natural products and important part of our food. Polysaccharides have been reported to exert anti-hyperlipidemic effect by increasing the serum insulin level that reduce the blood glucose level and enhance glucose tolerance. Polysaccharide rich extract from pumpkin (Cucurbita moschata Duchesne ex poir) was reported as α-glucosidase inhibitor. Pumpkin’s protein-bound polysaccharide was reported to increase the serum insulin level and hence, exert hypoglycemic effects.\textsuperscript{330} Doses of 150-300 mg/kg body weight of water-soluble polysaccharide from the root of Ophiopogon japonicus (L.f.) have been reported to increase the insulin level by repairing the pancreatic islets in STZ-induced diabetic rats.\textsuperscript{331} The fructans having β-(1→2)-fructosyl residues from root of Liriope spicata var. prolifera were reported have hypoglycemic and hypolipidemic activities.\textsuperscript{332} Treatment with polysaccharide fraction of Hedysarum polybotrys, Sonneratia alba, Bupleurum smithii var. parvifoliu, Portulaca oleracea L., and Salicornia herbacea, Pleurotus florida (200 and 400 mg/kg) was reported to decrease glucose, TC, and TG levels significantly. Moreover, it was found to decrease MDA, and NO levels, and increase the SD, CAT and GSH levels. Polysaccharides from these plants were found to promote pancreatic β cells and liver hepatocytes and ameliorate T2DM due to their anti-oxidative and anti-inflammatory properties.\textsuperscript{333} Pseudostellaria heterophylla is a traditional Chinese medicine, extensively used to treat diabetes. The polysaccharide (950 ~ 210 kDa) from the plant, composed of galacturonic acid, glucose, galactose and arabinos (100 ~ 400 mg/kg) was found to be effective in T2DM. It improves the...
insulin tolerance and inhibits TNF-α expression, elevates cytokine IL-10, and regulates adiponectin Acrp30 and leptin. Another herbal drug of Chinese traditional medicine i.e. tuberous root of Liriope spicata var. prolifera has been widely used to treat T2DM. Two new polysaccharides and the total polysaccharides decreased the fasting blood glucose and improved insulin resistance and serum lipid metabolism significantly in diabetic mice. These polysaccharides also reported to decrease the hepatocyte hypertrophy and lipid accumulation in the mice liver. These are reported to inhibit hepatic gluconeogenesis and increase the glycolysis and contents in liver. These polysaccharides were found to control T2DM by increasing the IR, IRS-1, PI3K and PPAR-γ expression. β-Glucans from Rhynchelytrum repens rich in arabinose, glucose, xylose, and traces of rhamnose and galactoses were reported to decrease blood sugar.333 Polysaccharide isolated from Coptis chinensis Franch (Ranunculaceae) reduced the fasting blood glucose levels (p<0.01) TG and TC (p<0.05). It was also reported to increase GSH-Px, SOD, and CAT activities, and decrease the serum GSH and MDA levels (p<0.01). Its anti-oxidant and anti-diabetic mechanism involves the modulation of JNK/IRS1/PI3K pathway.333,334,335 Dioscorea hispida tuber, Ocimum basilicum seeds and Radix ophiopogonis contain the polysaccharides and were reported to decrease blood glucose level in T2DM and also inhibit gut glucose absorption. The antidiabetic activity was mainly due to inhibition of PTP-1B. Mycaminose (PubChem CID: 53477765) isolated from fruits of Syzygium cumini reported to be potent α-glucosidase and PTP1B inhibitors.336 A dose of 40 mg/kg/day of antcin K have been reported to have same efficacy as of metformin (300 mg/kg/day) and fenofibrate (250 mg/kg/day), hence having efficacy to treat T2DM and hyperlipidemia. It was reported to increase the GLUT4 expression levels significantly and decrease the G6Pase mRNA levels, hence to control the blood glucose levels. It was reported to increase AMPK activation and inhibit the FAS expression. It also increases PPARγ expression and decrease SREBP1c expression resulting in depleted levels of TG and TC.339 A bioactive component 6-gingerol from Zingiber officinale (ginger) was reported to inhibit adipogenesis through activation of Wnt/β-catenin signaling pathway and increasing phosphorylations of GSK-3β in 3T3-L1 cells.340 Allicin (PubChem CID: 65036), isolated from water soluble fraction of Tillandsia usneoides (Linn.) showed hypoglycaemic activity in fasting healthy mice.341 Selaginellin derivatives (PubChem CID: 46885723) (5 μM), isolated from Selaginella tamariscina were reported to be potent inhibitors of PTP1B and stimulate glucose uptake in 3T3-L1 adipocyte cells.342 2-Hydroxy 4-methoxy benzoic acid isolated from roots of Hemidemus indicus (Linn.) R.Br. was reported to increase insulin secretion and activate glycogen synthase, hence controlled the blood glucose levels in STZ induced diabetic rats.343 Pinitol (PubChem CID: 5319730), a compound identified from leaves of Bougainvillea spectabilis Comm. Ex Juss has been reported to have anti-diabetic activity. It exerts hypoglycaemic effect by inhibiting α-amylase and increasing the glucose-dependent insulin secretion from beta cells and increasing glucose uptake in the liver through activation of the PI3K/Akt signaling pathway.344

**OTHERS COMPOUNDS**

Many other phytochemicals, which have not been covered in the above classification, were also reported to possess antidiabetic properties. Coagulanolide and withanolide (PubChem CID: 53477765) isolated from fruits of Withania coagulans Linn. were reported to inhibit post prandial glucose in sucrose loaded normoglycemic rats as well as STZ induced diabetic rats as compared to metformin. Theses compounds promoted the beta cells regeneration or protected the beta cells from destruction. These compounds also reported to increase insulin secretion or activate insulin receptors and increase the peripheral glucose consumption.336 Chicoric acid was reported to be a potent ROS scavenger and also stimulator of the AMPK pathway. It was also shown to up-regulate PGC-1α expression and inhibits the insulin/Akt/mTOR pathway.337 Artemisia capillaris components i.e. coumarins, esculetin, scopoletin were reported to be potent α-glucosidase and PTP1B inhibitors. Hence, methanol extract of A. capillaris was reported to be preventive agents for T2DM.338 A dose of 40 mg/kg/day of antcin K have been reported to have same efficacy as of metformin (300 mg/kg/day) and fenofibrate (250 mg/kg/day), hence having efficacy to treat T2DM and hyperlipidemia. It was reported to increase the GLUT4 expression levels significantly and decrease the G6Pase mRNA levels, hence to control the blood glucose levels. It was reported to increase AMPK activation and inhibit the FAS expression. It also increases PPARγ expression and decrease SREBP1c expression resulting in depleted levels of TG and TC.339 A bioactive component 6-gingerol from Zingiber officinale (ginger) was reported to inhibit adipogenesis through activation of Wnt/β-catenin signaling pathway and increasing phosphorylations of GSK-3β in 3T3-L1 cells.340 Allicin (PubChem CID: 65036), isolated from water soluble fraction of Tillandsia usneoides (Linn.) showed hypoglycaemic activity in fasting healthy mice.341 Selaginellin derivatives (PubChem CID: 46885723) (5 μM), isolated from Selaginella tamariscina were reported to be potent inhibitors of PTP1B and stimulate glucose uptake in 3T3-L1 adipocyte cells.342 2-Hydroxy 4-methoxy benzoic acid isolated from roots of Hemidemus indicus (Linn.) R.Br. was reported to increase insulin secretion and activate glycogen synthase, hence controlled the blood glucose levels in STZ induced diabetic rats.343 Pinitol (PubChem CID: 5319730), a compound identified from leaves of Bougainvillea spectabilis Comm. Ex Juss has been reported to have anti-diabetic activity. It exerts hypoglycaemic effect by inhibiting α-amylase and increasing the glucose-dependent insulin secretion from beta cells and increasing glucose uptake in the liver through activation of the PI3K/Akt signaling pathway.344

**Table 1:** Table is showing natural product, their mode of action, and effective in *vitro* and *in vivo* doses.

<table>
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<tr>
<th>S No</th>
<th>Compound Name</th>
<th>Mode of action</th>
<th>Effective Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>In vitro</td>
<td>In vivo</td>
</tr>
<tr>
<td>Alkaloids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Berberine</td>
<td>AMPK Activation and GLUT-4 Synthesis</td>
<td>25 μg/ml</td>
</tr>
<tr>
<td>2.</td>
<td>Boldine</td>
<td>Stabilize NO Production and eNOS Phosphorylation</td>
<td>344 µM</td>
</tr>
<tr>
<td>3.</td>
<td>Palmatine</td>
<td>Activate expression of PPARα and induction of GLUT-4</td>
<td>7.7 µg/ml</td>
</tr>
<tr>
<td>4.</td>
<td>Jatrohizine</td>
<td>Increase cAMP Synthesis Activation of PPARα and GLUT-4</td>
<td>227 µM/L</td>
</tr>
<tr>
<td>5.</td>
<td>Trigoneline</td>
<td>Increase GLUT-4 Expression, decrease TNF-α and activation of PPAR</td>
<td>125 µM</td>
</tr>
<tr>
<td>6.</td>
<td>Vindoline</td>
<td>Inhibit protein tyrosine phosphatase-1B</td>
<td>50.2 µM/L</td>
</tr>
<tr>
<td>7.</td>
<td>Catharanthine</td>
<td>Increase hexokinase activity and decrease glucose-6-phosphatase and fructose-6-phosphatase activity</td>
<td>100mg/kg</td>
</tr>
<tr>
<td>8.</td>
<td>Piperidine</td>
<td>Decrease PEPCK expression</td>
<td>2.72mg/kg</td>
</tr>
<tr>
<td>9.</td>
<td>Aegeline</td>
<td>Enhanced GLUT-4 translocation, activate PAK-1 and inhibit activity of Akt and Rac 1</td>
<td>20mg/kg</td>
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<tr>
<td>12. Chrysine</td>
<td>Formononetin</td>
<td>Increases expression of GLUT4 mRNA, adiponectin, PPAR-γ, FABP4 and LPL.</td>
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<td>Increases expression of GLUT4 mRNA, adiponectin, PPAR-γ, FABP4 and LPL.</td>
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### Phenolics

**37. Cyanidin-3-galactoside**
- Increases expression of ABCA-1, PPAR-α, Y C/EBPα gene, decreases expression of ICAM1, MCP1 and TGFβ1, activates NF-kB and LXR-α.

**40. Cinnamic acid**
- Inhibit NF-κB activation, reduces expression of TNF-α, MCP -1

**42. Gallic acid**
- Increases of PPAR-Y target proteins expression and fatty acid binding protein

**43. Caffeic acid**
- Modulates Nrf 2 expression

**44. p-Coumaric acid**
- Inhibit adipogenesis, GDH activity and PPAR-Y expression

**45. Chlorogenic acid**
- Reduces HMGT–CoA reductase activity and increases LPL activity in plasma

### Anthocyanins

**36. Pelargonidin**
- Inhibit phosphorylation of MAPks i.e. p38, JNK andERK1/2 and pro-inflammatory cytokines (TNF-α, IL-1β).

**38. Delphinidin**
- Increases expression HNF-1α

**39. Malvidin**
- Increases expression of CPT-1 and PPAR-α and decrease expression of FAS and SREBP-1c, increase AMPK/ACC and Akt/FOXO1 signalling.

### Stilbenes

**47. Resveratrol**
- Modulation of AMPK, SIRT1 and PGC-1α expression via LKB 1

**48. Pterostilbene**
- Increases GLUT-4 protein expression and Akt phosphorylation

### Coumarins

**49. Coumarin**
- Decreases the plasma glucose, HbA1c, G-6Pase levels and increase of insulin, haemoglobin , G-6Pase and F-1,6-BPase levels

**50. Esculin**
- DecreaseS TG, CH, LDL, IL-1, IL-6, ICAM-1, NO, NGAL levels.

**51. Cinnamon**
- Decreases Scr and glucose levels, increases creatinine clearance

### Xanthones

**52. Mangiferin**
- Decreases FBS, TC, TG, LDL, VLDL and elevated HDL levels

**53. Cudraticrixanthone**
- Prevents NF-κB and JAK/STAT activation, cytokines induced NO production, INOS expression

### Triterpenes

**54. Oleanolic acid**
- Inhibits IFN-γ, induce NO production

**55. Glycyrrhetic acid**
- Increases AMPK, SIRT1 and Mn–SOD expression.

**56. Arjunoic acid**
- Inhibits intracellular RNS and ROS formation in spleen tissue, decreases TNF -α levels, increases IL-2 and IFN-Y levels

**57. 4-secofriede lan-3-oic acid**
- Reduces ALP and AST activities

**58. Asianic acid**
- Increases GLUT-4 expression and Akt phosphorylation

**59. Tormentic acid**
- Increases AMPK and Akt phosphorylation, increases GLUT-4 translocation

**60. Maslinic acid**
- Activates Akt , phosphorylate IRβ-subunit and GSK3β

**61. Betulinic acid**
- Inhibits PGC-1α, PEPCK and G6Pase gene expression, increases CAMKK, AMPK and ACC phosphorylation

**62. Ganoderic acid B**
- Reduces GOT and GPT levels in serum

**63. Ganoderic acid A**
- Decreases GPT activity

**64. Celestrol**
- Activates PGC-1α, inhibits production of NO synthase

### Quinones

**46. Embelin**
- Reduced TNF–α activity by inhibiting TNF-α converting enzymes

**47. Embelin**
- Silencing p38 and PKC-δ gene, activating AMPK-PGC-1α-Sirt3 signalling pathway and increase GLUT-4 translocation.

**48. Diosmin**
- Increase expression of PPAR-Y2, activate Akt in HepG2 cells, and down regulate TNF-α, ICAM-1, VEGF and eNOS.

**49. Embelin**
- Activates PPAR-Y, C/EBPα and increases GLUT-4 translocation by activating Akt and AMPK pathway, decrease NF-kB and I-kB-α kinase activity.

**50. Pinobanksin**
- Reduces HMGT-CoA reductase activity and increases LPL activity in plasma

**51. Cinnamon**
- Decreases Scr and glucose levels, increases creatinine clearance

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<td>Pterostilbene</td>
<td>Increases GLUT-4 protein expression and Akt phosphorylation</td>
<td>8 µM</td>
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<td>Embelin</td>
<td>Reduced TNF–α activity by inhibiting TNF-α converting enzymes</td>
<td>15 µM</td>
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<tr>
<td>Diosmin</td>
<td>Silencing p38 and PKC-δ gene, activating AMPK-PGC-1α-Sirt3 signalling</td>
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<td>Pinobanksin</td>
<td>Decreases HMGT-CoA reductase activity and increases LPL activity in</td>
<td>10 µM</td>
</tr>
<tr>
<td>Diosmin</td>
<td>Increase expression of PPAR-Y2, activate Akt in HepG2 cells, and down</td>
<td>10-20 µM</td>
</tr>
<tr>
<td>Anthocyanins</td>
<td>Inhibit phosphorylation of MAPks i.e. p38, JNK andERK1/2 and</td>
<td>2.73 mg/ml</td>
</tr>
<tr>
<td>Pelargonidin</td>
<td>Increases expression of ABCA-1, PPAR-α, Y</td>
<td>50 µM</td>
</tr>
<tr>
<td>Delphinidin</td>
<td>Increases expression HNF-1α</td>
<td>100 µM</td>
</tr>
<tr>
<td>Malvidin</td>
<td>Increases expression of CPT-1 and PPAR-α and decrease expression of</td>
<td>50 µM</td>
</tr>
<tr>
<td>Cinnamic acid</td>
<td>Inhibit NF–κB activation , reduces expression of TNF-α, MCP -1</td>
<td>100 µM</td>
</tr>
<tr>
<td>Anacardic acid</td>
<td>Activates AMPK, increase GLUT-4 translocation into cell membrane and</td>
<td>100 µg/ml</td>
</tr>
<tr>
<td>Gallic acid</td>
<td>Increases of PPAR-Y target proteins expression and fatty acid binding protein</td>
<td>5 µM</td>
</tr>
<tr>
<td>Caffeic acid</td>
<td>Modulates Nrf 2 expression</td>
<td>100 µM</td>
</tr>
<tr>
<td>p-Coumaric acid</td>
<td>Inhibit adipogenesis, GDH activity and PPAR-Y expression</td>
<td>10 µg/ml</td>
</tr>
<tr>
<td>Chlorogenic acid</td>
<td>Reduces HMGT–CoA reductase activity and increases LPL activity in</td>
<td>1 mM</td>
</tr>
<tr>
<td>Embelin</td>
<td>Reduced TNF–α activity by inhibiting TNF-α converting enzymes</td>
<td>15 µM</td>
</tr>
</tbody>
</table>
Table 1. These compounds can be categorized into inhibitors reported for their selective activities toward specific targets.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Other Systemic Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysaccharides</td>
<td>Decreases blood sugar</td>
</tr>
<tr>
<td>Saponins</td>
<td>Activates PPAR-A</td>
</tr>
</tbody>
</table>

**Other Compounds**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choric acid</td>
<td>Stimulates AMPK pathway and inhibits insulin/Akt/mTOR pathway</td>
</tr>
<tr>
<td>Scopoletin</td>
<td>Inhibits α-glucosidase and PTP1B</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Increases GLUT-4 expression and AMPK activation</td>
</tr>
<tr>
<td>Allicin</td>
<td>Possess hypoglycaemic activity via AMPK activation</td>
</tr>
<tr>
<td>Pinitol</td>
<td>Inhibits α-amylase and increases glucose dependent insulin secretion from beta cells</td>
</tr>
</tbody>
</table>

**Conclusion**

Treatment of T2DM requires multidisciplinary approaches and beside the medicinal treatment it requires dietary and lifestyle management. A number of options are available for the physicians to lower the blood glucose. However, number of anti-diabetic drugs may also lead to cardiovascular problems. Natural products are being used from a long time to treat various kinds of disorders including T2DM. A very vast literature is available that describes number of anti diabetic plants and their compounds with different types of mechanism of action. However, their credibility is less due to very less number of clinical trials. Still the available scientific evidences increased the use of herbal products in developed countries. The systemic research reviews that include metabolomics and nutrigenomics may further increase the credibility of these drugs. As a number of anti-diabetic compounds have been reported from regular food products and some herbal products may be included in the dietary products of T2DM patients to study nutrigenomics and metabolomics of the T2DM pateints. Compounds isolated from various herbs and plants have been reported for their selective activities toward specific targets (Table 1). These compounds can be categorized into inhibitors of 11β-Hydroxysteroid dehydrogenase type 1, glucocorticoids receptor, glucagon receptor, glycogen phosphorylase, fructose-1,6-biphosphatase, α-glucosidase, aldose reductase, SGLT2 and PTP1B enzymes or agonists of AMPK, AKT, PPARα, PGC-1α, IRS1, PI3K and other important targets to treat T2DM. These compounds can be used alone or in different combinations to...
increase their efficacy. However, cost and difficulty of purification of these compounds prevent their availability for further research and clinical trial. Moreover, high in vivo dose and limited oral availability also limited the use of these compounds. Still, there are lots of promising compounds need to be studied in vivo, alone or in combination with compounds. For example, andrographolide at dose of 10 mg/kg body weight was found to reduce secondary complications of DM II along with activation of PI3-K and AMPK signaling pathways. Piperidine decrease PEPCK expression whereas, aegeline stimulate PI3-kinase-Rac1-PAK1-cofilin pathway. Flavonoids are natural antioxidants tat reduce TNF-α levels an inhibitor of IRS1 and apigenin and chrysin have been also reported to increase AMPK phosphorylation. Myricetin increase the phosphorylation of IR, IRS-1 and Akt that improve translocation of GLUT-4. Embelin and morin were reported to phosphorylation of IR, IRS-1 and Akt that improve translocation of GLUT-4. Embelin and morin were reported to reduce in vivo NF-kB activation. Another important compound, glycyrrhizic acid activates the AMPK pathway that increase glucose uptake. Celastrol is known activator of PGC-1α that also inhibits the production of NO synthesis, hence decrease oxidative stress and increase Glut-4 translocation. Cucurbitanes, dehydroametanolic and dehydratroculosolic acid activates the AMPK signaling pathway. Well studied compounds mogroside V and RgI activates PI3K/Akt pathway and efficiently control the increased glucose levels. Reservatrol was found to be endowed with anti-oxidant and anti-diabetic activities through activation of AMPK. It also activates the sirtuin deacetylase and increase the life span. Hence, interest in this compound has been renewed recently. Chemical structure of galegine is quite similar to the metformin, a standard drug being used in DM II. Number of polyphenols and anthocyanins are effective antagonists of intestinal α-glucosidase/maltase and can be used with starch rich diets to reduce glycaemia. Harmin is an antagonist of DYRK1A and monoamine oxidases. It also mediates human β cell differentiation and proliferation.

Synthesis of these compounds may reduce the cost and increase their availability for further research. SGLT2 inhibitor, phlorizin is an example which has been modified to increase its efficacy into other derivatives like sergliflozin, canagliflozin, remogliflozin, and dapagliflozin. Some plants have been reported to contain multiple molecules having different types of anti-diabetic mechanism of action. *T. cordifolia*, *P. marsupium*, *C. moschata*, *M. charantia* etc. contains multiple compounds having anti-diabetic activity with different mechanism of actions. Hence, to study the mechanism of action of natural compounds, specifically showing promising activity, may lead toward the development of better anti-diabetic drugs or provide a base to develop better anti-diabetic molecules using medicinal chemistry approaches. However, more investigations must be carried out to explore the anti-diabetic mechanism of action at cellular and molecular level for future applications.

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**DISCLOSURES**

All authors have no conflict of interest to declare.

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