Current Topics in Medicinal Chemistry, 2016, *16*, 2532-2542

Therapeutic Potentials of Triterpenes in Diabetes and its Associated Complications

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Abstract: Diabetes is a major chronic metabolic disorder globally and around of 285 million people are affected by the disease and the number is expected to double in the next two decades. The major focus of anti-diabetic therapies is to enhance insulin production, sensitivity and/or reduce the blood glucose level. Although several synthetic drugs have been developed as antidiabetic agents but their utility has been hampered due to their side effects and poor efficacy. In this scenario, research on natural products has been gained importance due their safety profile in toxicity studies. Terpenoids belong to an important class of natural products and several terpenoids have been reported as antidiabetic agents. Some of them are under various stages of pre-clinical and clinical evaluation to develop them as antidiabetic agents. These agents can inhibit enzymes responsible for the development of insulin resistance, normalization of plasma glucose and insulin levels and glucose metabolism. Triterpenes can act as promising agents in the treatment of diabetic retinopathy, neuropathy and nephropathy or in impaired wound healing by inhibiting several pathways involved in the diabetes and associated complications. However, efforts in understanding the biological actions and clinical studies involving the applications of triterpenes in treating diabetes are very limited. Hence, special attention is imperative to explore the therapeutic potential of these compounds and provide new information to the scientific community. This review aims to provide the recent advances in triterpenes chemistry, its derivatives, biological interventions and its therapeutic applications with special emphasis on diabetes and its associated disorders.

Keywords: Triterpenes, Diabetes, Blood glucose, Insulin, hyperglycemia.

Received: February 12, 2016 **Revised: February 24, 2016** **Accepted: February 27, 2016**

1. INTRODUCTION

Diabetes mellitus is an endocrine disorder characterized by chronic hyperglycemia, which results from an absolute or relative deficiency of resistance to insulin. According to the World Health Organization (WHO), 346 million people suffer from diabetes worldwide, whereas death rate due to this disease will expected to be double between 2005 and 2030.

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1873-5294/16 $58.00+.00

The increased morbidity and mortality diabetes mellitus is due to a poor glycemic control over a long period of time, which leads to progression of diabetic complications [1].

The incidence of mortality has been increased day by day because of uncontrolled diabetes in diabetic patients. There were so many mechanisms involved in pathogenesis of diabetic complications. Oxidative stress leads to imbalance between oxidants and antioxidant enzyme, which causes the activation of major pathways involved in the pathogenesis of complications [2]. Intracellular production of advanced glycation end products (AGEs) precursors [3]; Glycation is the non-enzymatic reaction between a protein and a reducing sugar, such as glucose and fructose [4] resulting in generating dicarbonyl compounds and finally advanced glycation end products [5]. AGEs also promote activation and expression of IL-6 and TGFβ1 via NF-κB dependent pathways (Fig. **1**)[6]. Evidence has shown that AGEs participate directly in the pathogenesis of diabetic complications by accumulation and cross linking of long lived proteins [7,8]. Increased flux through the polyol pathway characterized by increasing aldose reductase and accumulation of sorbitol content due to reduction of that glucose to sorbitol leading to cataract, retinopathy and peripheral neuropathy [9]. PKC is activated by intracellular hyperglycemia, it has a variety of effects on gene expression, vasodilator producing endothelial nitric oxide (NO) synthase (eNOS) is decreased, while the vasoconstrictor endothelin-1 is increased [10]. Increased hexosamine flux through the pathway can be increased by accelerating glucose entry or by inhibiting glycolysis distal to fructose-6-phosphate glucosamine-fructose-6-phosphate amidotransferase could cause insulin resistance and the complications of diabetes [11]. Glucose transporters are a wide group of membrane proteins that facilitate the transport of glucose over a plasma membrane are GLUT2, GLU4 and SGLT1 are membrane proteins plays an important role in glucose transport over a plasma membrane (Fig. **2**). Hyperglycemia was characterized by increase expression of GLUT 2 and SGLT 2 and decreased expression of GLUT 4 [12]. In insulin resistant conditions there was reduction in expression of PPARγ and mediated production of adiponectin, which are key factors to promote insulin sensitivity [13] (Fig. **2**).

Herbal medicines have been used for thousands of years in many ethnic cultures such as Indian, Chinese, Korean, and Mexican to treat and manage diabetes and its complications [14]. Although several synthetic drugs have been developed as antidiabetic agents but their utility has been hampered due to their side effects and poor efficacy. In this scenario, research on natural products has been gained importance due their safety profile in toxicity studies [15]. Terpenoids belong to an important class of natural products and several terpenoids have been reported as antidiabetic agents [16]. Some of them are under various stages of pre-clinical and clinical evaluation to develop them as antidiabetic agents. In this review, we critically discuss the potential utility of several terpenoids from various plants as antidiabetic agents. In addition, possible mode of action of triterpenoids in diabetes and associated complications is also discussed.

2. TRITERPENES

Terpenes are part of the largest group of biologically active plant products, which are chemically classified based on the number of isoprene subunits, $[C_5H_8]_n$ [where n = number of isoprene units]. Therefore, this group consists of hemiterpenes [C5], monoterpenes [C10], sesquiterpenes [C15], diterpenes [C20], sesterpenes [C25], triterpenes [C30], tetra-

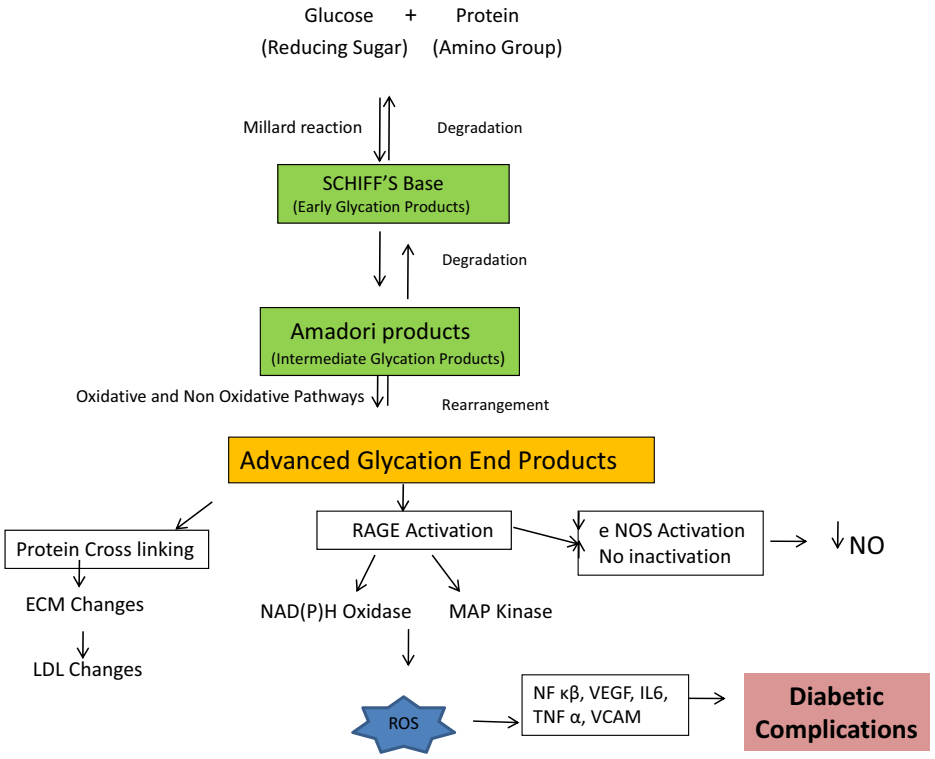

Fig. (1). Formation of AGEs and their involvement in diabetic complications.

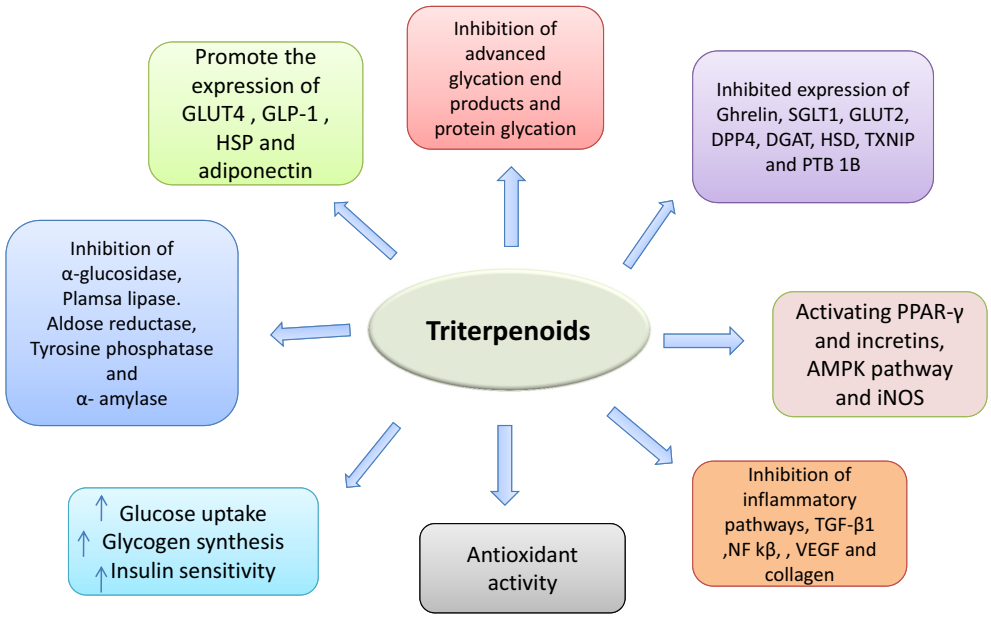

Fig. (2). Various mechanisms of actions of triterpenoids for their antidiabetic activity.

terpenes [C40] and polyterpenes polyterpenes [C_n]. Reports have shown that despite the wide distribution of terpenes in plant kingdom, most of these bioactive compounds have been found in higher plants [17,18].

Triterpenes are widely distributed in the plant and marine animal kingdoms, where they occur either in the free state, as esters, or as glycosides [saponins]. They are composed of six isoprene units $[C_5H_8]_6$ from mevanolic acid or deoxyxylulose phosphate, and are derived from the reductive coupling of two molecules of farnesyl pyrophosphate by squalene synthase. Some examples of isolated terpenoids are squalene derivatives, lanostanes, holostanes, cycloartanes, cucurbitanes, dammaranes, euphanes, tirucallanes, tetranortriterpenoids, quassinoids, lupanes, oleananes, friedelanes, ursanes, hopanes, serratanes, isomalabaricanes and saponins [19, 20].

3. TRITERPENES FROM MEDICINAL PLANTS AS ANTIDIABETIC AGENTS

Several traditional medicinal plants were reported for the treatment of diabetes and diabetic complications. Such as *Glycyrrhiza sps*, *Gymnema sps*, *Centella asiatica, Camellia sinensis, Crataegus sps* and *Olea europaea* due to the presence of bioactive pentacyclic triterpenoids, such as oleanolic acid, glycyrrhizin, glycyrrhetinic acid, ursolic acid, betulin, betulinic acid and lupeol (Fig. **3**). Triterpenoids worked against diabetic vascular dysfunction, retinopathy and nephropathy by multiple biological activities on glucose absorption, glucose uptake and insulin secretion [21].

Hamid *et al.* [22] reported that Panax ginseng, Panax quinquefolium, Panax notoginseng, Gynostemma pentaphyllum, Astragalus membranaceus, Momordica charantia and Ganoderma lucidum contains Tetracyclic triterpenoids, including the dammarane, cucurbitane, cycloartane, lanostane and protostane groups commonly used for the treatment of diabetes and its complications (Table **1**).

Agrimonia pilosa contains triterpenoid compounds could promote preadipocytes differentiation through activating PPAR-γ and downstream controlled genes. Triterpenes can promote the expression of PPAR-γ, CCAAT enhancer binding protein-α [C/EBP-α], and sterol regulatory element-binding protein 1 and significantly promote the expression of GLUT4 and adiponectin (Table **1** & Fig. **2**) [69].

Aralia taibaiensis contains triterpenoids and phenolics, reported to have antioxidant and anti-glycation effects [12]. The terpenoids isolated from the *Aralia taibaiensis* shown to have antioxidant activity against DPPH radical and antiglycation activity against hemoglobin-delta-gluconolactone [delta-Glu] assay, bovine serum albumin [BSA]-glucose assay and *N*-acetyl-glycyllysine methyl ester [GK peptide]-ribose assay [70,71].

Abelmoschus esculentus contains pentacyclic triterpene ester as adjuvant therapy for diabetic nephropathy. Chiung HP., 2016 [72] worked on diabetic renal epithelial to mesenchymal transition [EMT], which plays a critical role in fibrosis act by inhibits high glucose-stimulated vimentin, AT-1, TGF-β1, DPP-4 and recovers E-cadherin in tubular cells.

Anoectochilus elwesii contains a new oxygenated triterpene 3-β-*O*-olean-11,13 [18]-diene 23,28-dioic acid, works on insulin-resistant human HepG2 cells for stimulating glucose uptake activity (Table **1**) [73].

Astragalus radix contains triterpenes such astragalosides that acts on the formation of AGEs such as carboxy methyl lysine [CML]. These triterpenes can interrupt the interactions between reducing sugars and amino acids, thereby reducing formation of AGE and control the glycative stress by reduction of protein glycation process (Table **1**) [74].

Agrimonia pilosa contains triterpenoid compounds shown to targeting oxidative stress and postprandial hyperglycemia by scavenging the DPPH radical, ABTS radical and hydroxyl radical, β-carotene-linoleic acid assay and α-glucosidase inhibitory activities. There by it exhibiting re-

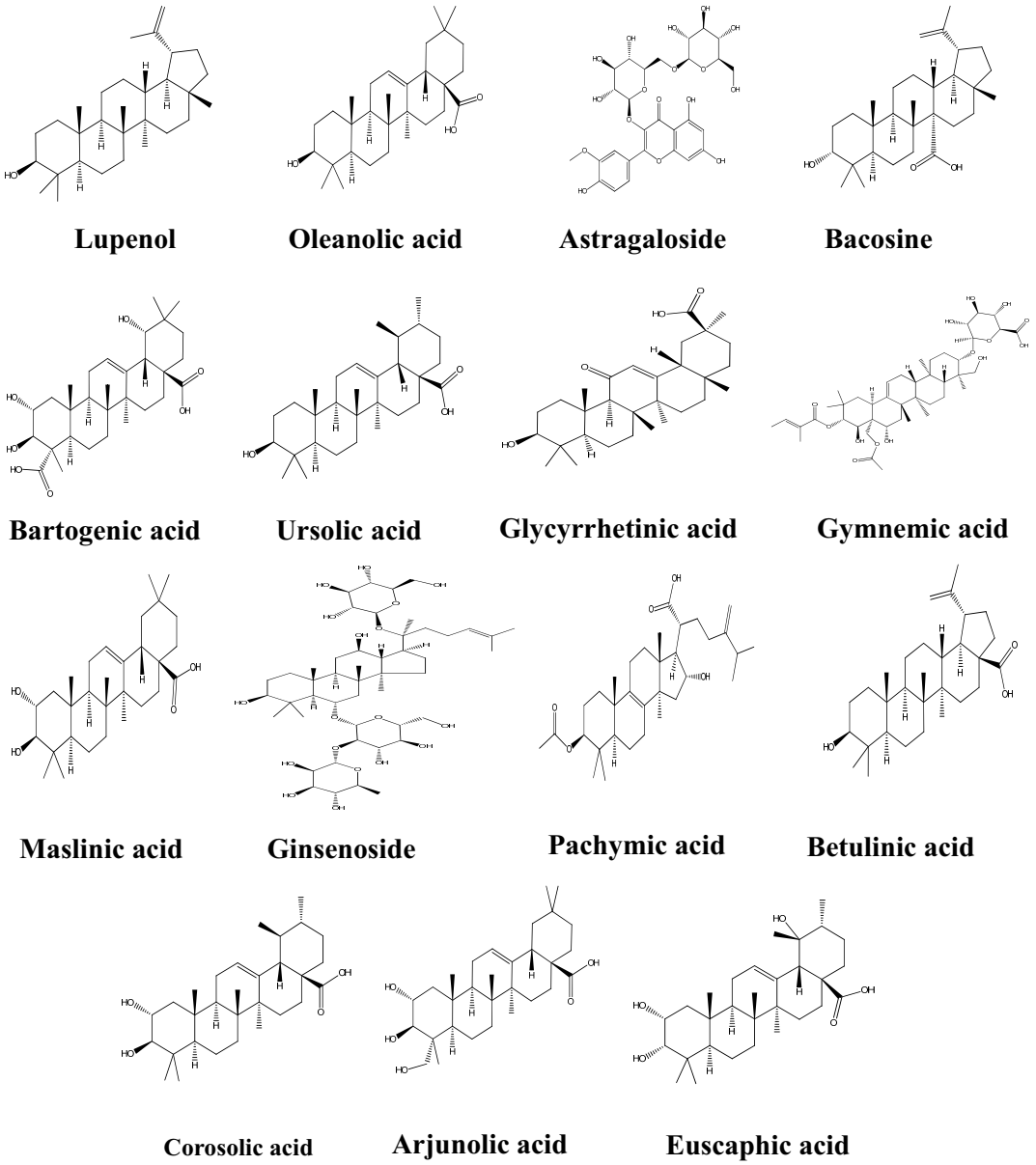

Fig. (3). Some of important triterpenoids with antidiabetic activity

markable potential value for the therapy of diabetes mellitus [75].

Bumelia sartorum root bark contains bassic acid, an unsaturated triterpene acid showed significant hypoglycemic activity altered glucose tolerance, increased significantly the glucose uptake process and glycogen synthesis in isolated rat diaphragm, increased plasma insulin levels mediated through enhanced secretion of insulin from the pancreatic beta-cells significantly in alloxan-diabetic rats (Table **1** & Fig. **3**) [76].

Bouvardia terniflora dried stem contains two triterpenes namely ursolic acid and oleanolic acid. The compounds lowered blood sugar levels in normal and alloxan-diabetic mice (Table **1** & Fig. **3**) [77].

Centella asiatica have asiaticoside, a terpenoid, which play a role of oxidative stress on the pathophysiology of diabetic neuropathy. The beneficial effect of asiaticoside is due to their involvement in the protective mechanism against painful stimuli by foot withdrawal reflex (Fig. **2**) [78].

Curcuma longa contains Tricyclic diterpenoid, Diterpenoids, Tetranorterpenoids, Triterpenoids in oil and leaves shown to have oxidative stress and antidiabetic activity [79].

Calotropis procera (Asclepiadaceae) root extract was investigated as an inhibitor of pancreatic lipase (PL) due to the presence of di-terpenoid fraction. It showed highest inhibition of pancreatic lipase in comparision with a standard inhibitor, Orlistat. Antihyperlipidaemic effects of *C. procera* root extract can be partly attributed to the inhibition of PL by di-terpenoids present in it [80]

Cleome droserifolia contains six terpenoids have been isolated from the aqueous and ethanolic extracts and were tested in cultured C2C12 skeletal muscle cells and 3T3-L1 adipocytes. *Cleome droserifolia* is attributed to significant

Table 1. Several antidiabetic triterpenods and their mechanism of actions.

Terpenoids	Source	Antidiabetic activity	References
Lupenol	*Aegle marmelos*	Antidiabetic action by β-cell protection, regeneration and normalise the lipid profile	[23,24]
Oleanolic acid	*Aralia elata*	Reduction in blood glucose levels	[25]
Astragaloside	*Astragalus membranaceus*	Decrease in renal AGEs formation	[26]
Bacosine	*Bacopa monniera*	Decreased blood glucose Levels by enhancing glucose utilization and protein glycation inhibition	[27,28]
Bartogenic acid	*Barringtonia racemosa*	Pancreatic α-amylase inhibition	[29]
11-keto-ursolic acid and 3-acetyl-11-keto-ursolic	*Bursera delpechiana*	Increased inhibitory potential On 11b-HSD1	[30]
Ursolic acid	*Campsis grandiflora*	Translocation of Insulin stimulated GLUT4	[31]
7b-hydroxy-3-oxo-d:afriedooleanan-28-oic Acid, astragaloside IV	*Celastrus vulcanicola*	Increased Phosphorylation of insulin receptors	[32]
Asiatic acid and Madecassic acid	*Centella asiatica*	Reduced the blood glucose levels and concomitantly increased serum insulin levels, Ameliorates obesity and glucose intolerance, Preserves pancreatic beta cell mass	[33,34]
Ursolic acid and Oleanolic acid	*Crataegus pinnatifida*	Normalize the total nitrate/nitrite and malondialdehyde levels, Decreased formation of AGEs Activate protein kinase C [PKC]	[35]
Corosolic acid, Pomolic acid	*Eriobotrya japonica*	Promotes 3*H*-glucose uptake, suppresses the differentiation and down-regulates the expression of PPAR-ɣ	[36,37]
Ursolic and Oleanolic acids, 3-epicorosolic acid methyl ester, Tormentic acid methyl ester and 2-ahydroxy-3-oxours-12-en-28-oic acid	*Eriobotrya japonica*	Promote insulin release by stimulating Pancreatic beta-cells, Increased inhibitory potential On 11b-HSD1	[38,39]
Aamyrin-3o-b-[5-hydroxy] ferulic acid	*Euclea undulate*	α-glucosidase inhibitory activity	[40]
2,3-seco-20[29]-lupene-2,3-dioic acid	*Fagus hayatae*	α-glucosidase inhibitory activity	[41]
Glycyrrhetinic acid	*Glycyrrhiza uralensis*	Improve glucose tolerance, Enhance insulin-stimulated glucose uptake Through PPAR-ɣ activation and induced MRNA levels of insulin receptor	[42]
Gymnemic acid	*Gymnema sylvestre*	Reduction of blood glucose, promotes insulin and inhibited GAPDH levels	[43,44]
Oleanolic acid	*Gypsophila oldhamiana*	Hepatic glycogen Phosphorylase [gp] catalyzing glycogenolysis	[45]

(Table 1) contd….

Terpenoids	Source	Antidiabetic activity	References
Hodulcin, Hodulosides and Jujuboside b	*Hovenia dulcis*	Sweetness inhibitors	[46]
Oleanane- and ursane	*Ilex paraguariensis*	Antioxidant, antiglycation, anti-obesity activity	[47,48]
Ilexgenin A	*Ilex pubescens*	Supression of TXNIP	[49]
Corosolic Acid [1-hydroxyursolic acid]	*Lagerstroemia speciosa*	Exhibits hypoglycemic activity by α-glucosidase inhibiting activity.	[50,51]
3β-taraxerol	*Mangifera indica*	Increase glycogen synthesis through the activation of PKB and activates glucose transport by inducing the activation of GLUT4.	[52]
Maslinic acid	*Olea europaea*	Reduces blood glucose levels by inhibiting glycogen phosphorylase.	[53]
Ginsenoside	*Panax ginseng*	Increased Glucose uptake by activation of AMPK	[54]
Oleanolic and Ursolic acids	*Phyllanthus amarus*	Inhibited pancreatic α-amylase	[55]
Pistagremic Acid,	*Pistacia chinensis*	α-glucosidase inhibitory activity	[56]
Platycodin	*Platycodon grandiflorum*	Inhibit intracellular TG accumulation, down-regulation of PPAR-γ expression by binding to target DNA sequence	[57]
Senegins	*Polygala senega*	Reduction in blood glucose levels	[58]
Tormentic acid and Asiatic acid	*Potentilla biscolor*	Hepatic glycogen Phosphorylase [gp] catalyzing glycogenolysis	[59]
Oleanolic acid, Maslinic acid, Asiatic acid, Ursolic acid	*Protium heptaphyllum*	Decreased glucose, triglycerides, glycogenolysis, increased insulin transduction, β-cell proliferation	[60,61]
Lupeol and Lupenone	*Pueraria lobata*	Inhibits intracellular ROS generation	[62]
Ursane	*Rhododendron brachy-carpum*	Inhibitory activity against PTP 1B	[63]
Euscaphic acid and p-coumaroylursolic acid	*Sanguisorba tenuifolia*	α-glucosidase inhibitory activity	[64]
Lupane	*Sorbus commixta*	Inhibitory activity against PTP 1B	[65]
Ursolic acid, Orosolic acid	*Symplocos panicu-Lata*	Inhibitory activity against PTP 1B	[66]
Arjunolic acid	*Terminalia arjuna*	Reduces oxidative stress, hyperglycemia, membrane disintegration, decreased the level of serum pro-inflammatory TNF α	[67]
Corosolic acid, Pomolic acid, Ilekudinol a and b	*Weigela subsessilis*	Inhibitory activity against PTP 1B Stimulates glucose uptake	[68]
Ziziphin, Jujubasaponins	*Ziziphus jujuba*	Sweetness inhibitors	[46]

insulin-like effects in peripheral tissues leads to a potent antihyperglycemic agent [81].

Celastrus vulcanicola and *Maytenus jelskii* root barks contains friedelane-type triterpenes that were isolated to have potential therapeutic use in insulin resistant states [82].

Eriobotrya japonica contains ursolic, euscaphic, and corosolic acids which are responsible for the improvements in the adipokine profile and insulin sensitivity, to modify weight gain or either hepatic or plasma lipids [83], suppress fat accumulation and proliferation associated with suppressing PPARγ and C/EBPα expression (Table **1**, Figs. **2** & **3**) [84].

Fructus Corni contains total triterpene acid that acts on upregulation of the endothelin [ET] pathway is involved in impairment of vascular relaxation and early retinopathy in

diabetic rats in terms of pharmacological properties resembling the endothelin receptor antagonist CPU0213 and aminoguanidine a special antagonist for advanced glycation end-products [AGE] and inducible nitric oxide synthase [iNOS]. Total triterpene acid is effective in normalizing expression of the ET system and iNOS in early diabetic retinopathy and vasculaopathy (Table **1**, Figs. **2** & **3**) [85].

Momordica charantia possesses potential biological and pharmacological activities including antidiabetic, anti-obesity due to the presence of the main active constituent's charantin, a cucurbitane-type triterpenoid [86].

Momordica charantia [Cucurbitaceae], is a medicinal herb and reported to have hypoglycemic effects in animal models and humans. Triterpenoids are the main constituent of the fruit that curbitanetriterpenoids (*Mormodicoside S* and *karavilosede XI*) are capable of stimulating AMPK activity, favoring GLUT4 translocation, weight loss, and metabolic control [87].

Momordica cymbalaria root contains oleanane type triterpenoid saponin and reported to have potential neuroprotective effect in diabetic peripheral neuropathy with respect to neuropathic analgesia, improvement in neuronal degenerative changes, and significant antioxidant activity. Hypoglycemia is due to insulin sensitivity in Streptozotocin induced diabetic rats by promoting glucose uptake activity [88]. And showed significant decrease in tail immersion latency time and increase in pain sensitivity, there was improvement in the myelination and degenerative changes of the nerve fiber. Antioxidant activity of triterpenoids is by increase in superoxide dismutase, catalase activity, and decrease in lipid peroxidation in the nerves [89].

Ocimum kilimandscharicum, Ocimum tenuiflorum and *Ocimum gratissimum* contains monoterpenes and sesquiterpenes, particularly eugenol reported to have anti-glycation and inhibition of advanced glycation end products formation by binding to ε-amine group on lysine, protecting it from glycation. Eugenol can reduce in blood glucose due to inhibition of α-glucosidase but no effect on insulin and glycated hemoglobin levels [90].

Olea europaea and *Kalopanax pictus* and many plant food and medicinal herbs contains Oleanolic acid, which is endowed with a wide range of pharmacological properties majorly diabetes and diabetes complications by improving insulin response, preserving β-cells functioning and directly modulate enzymes connected to insulin biosynthesis, secretion, signaling and interacting with important transduction pathways, blocks NF-kB, the polyol pathway, AGEs production, and hyperlipidemia [91].

Pelliciera rhizophorae reported to have *α*-glucosidase inhibitory activity due to the presence of triterpenes like ursolic acid, oleanolic acid, betulinic acid. These triterpenes bind at the same site that acarbose in the human intestinal α-glucosidase and competitive type of inhibition against α-glucosidase [92].

Potentilla fulgens contains five terpenes, namely, hyptadienic acid, tormentic acid, rosamultic acid, 2α,19α-dihydroxy-3-oxo-12-ursen-28-oic acid β-D-glucopyranoside ester and kajiichigoside F1 for the first time from this plant. Among these hyptadienic acid, which is an A-ring contracted triterpenoid, was found to be the most potent against α-glucosidase. This suggests that the A-ring contracted triterpenes may serve as a class of triterpenes with α-glucosidase inhibitory activity [93]

Protorhus longifolia consists of two lanostane triterpenes [γ-hydroxylanosta-9,24-dien-21-oic acid, methyl-γ-hydroxylanosta-9,24-dien-21-oate]. The triterpenes effectively inhibited the activities of lipid digestive enzymes [pancreatic lipase, cholesterol esterase] stimulated glucose uptake in both 3T3-L1 and C2C12 cells. The triterpenes improved the activity of heat shock protein 70 [HSP70] their anti-protein aggregation activity using malate dehydrogenase [MDH] aggregation suppression [94].

Primula denticulate Sm. [Primulaceae] containing triterpenoid saponin are 3-*O*[β-D-xylopyranosyl[1 → 2]-*β*-D-glucopyranosyl-[1 → 4]-α-L-arabinopyranosyloxy]-16α-hydroxy-3β,28-epoxy olean-30-al reported to possesses potential glucose lowering properties against STZ-induced diabetic rats [95].

Poria cocos contain triterpenes dehydrotumulosic acid and pachymic acid had anti-hyperglycemic effect by reduce postprandial blood glucose levels in db/db mice via enhanced insulin sensitivity irrespective of PPARγ [96].

Salacia oblonga contains diterpene and triterpenes isolated from the ethyl acetate portion and were found to be responsible component for the hypoglycemic and hyperinsulinemic effect level in sucrose and maltose loaded rats. It also had anti oxidant activity and inhibitory activities on α-glucosidase and aldose reductase [97].

Syzygium aromaticum derived oleanolic acid and maslinic acid which use various mechanisms to lower blood glucose concentrations in experimental diabetes by reduction in blood glucose levels, inhibitory effects on the activity of α- amylase, α-glucosidase and sucrase , reduced plasma ghrelin concentrations, decreases in ghrelin, SGLT1, GLUT2, α-amylase and α-glucosidase expression in the gastrointestinal tract, reductions in MDA concentrations and increases in SOD and GPx by comparison with the STZ-diabetic control. This was followed by significant improvements in the antioxidant status in the rats suggesting that these triterpenes could, by preventing chronic postprandial hyperglycemia, prevent the onset of the development of diabetic complications [98].

Scleroderma aurantium contains a triterpene, 3,25-Dihydroxy-22-acetoxyl-lanosta-8,23-diene which is reported to have antihyperglycemic activity due to its inhibitory activity against α-glucosidase enzyme involved in diabetic complications [99].

Viburodorol A is a triterpene present in *Viburnum odoratissimum* and reported to have antihyperglycemic activity due to stimulate glucose absorption in insulin resistant HepG2 cells [100].

Trans-anethole (TA) a terpenoid and a principle constituent of many essential oils from medicinal plants shown significant reduction in the levels of plasma glucose, glycosylated haemoglobin (HbA1c) and increase in the levels of insulin and haemoglobin (Hb). Altered levels of hexokinase, glucose-6-phosphate dehydrogenase, glucose-6-phosphatase

and fructose-1,6-bisphosphatase in the liver and kidney of diabetic rats [101].

The known triterpenes oleanolic and ursolic acid showed activity against diabetic complications might be due to its effect on expression of aldose reductase and SDH. The suppression is caused by aldose reductase and SDH decreases endogenous AGE generation as well as carbonyl stress involved in progression of diabetic complications [102].

Ursolic acid is a triterpene compound derived from the berries, fruits, leaves and flowers of many medicinal plants. Diabetes induced glomerular hypertrophy and type IV collagen accumulation in the kidneys and were found to be markedly ameliorated suppressed diabetes induced activations of STAT-3, ERK1/2 and JNK pathways, but not the diabetes-induced activation of the p38 pathway leads to diabetes-induced over expression of iNOS in the renal cortex [103]. Inhibition of DGAT showed a marked reduction in hepatic triglyceride in HFD-induced obese mice [104]. Ursolic acid significantly reduced expressions of DGAT in both mRNA and protein levels, which might also be involved in the hepatic triglyceride deposition.

Maslimic acid is a triterpenoid showed to have effect on diabetic nephropathy by controlling the blood glucose levels and alter the pathways involved in diabetic nepharopathy such as polyol pathway and advanced glycation end products [105].

SUMMARY AND FUTURE DIRECTIONS

Diabetes has been considered as a global health burden by World Health Organization (WHO) and it represents one of the leading causes of mortality and morbidity worldwide. Although several synthetic drugs have been developed as antidiabetic agents but their utility has been hampered due to their side effects and poor efficacy. In this scenario, research on natural products has been gained importance due their safety profile in toxicity studies. Terpenoids belong to an important class of natural products and several terpenoids have been reported as antidiabetic agents. Fig. (**1**) showed that various molecular mechanisms involved in the diabetes and progression of diabetic complications by inhibit glucose absorption, glucose uptake, insulin secretion, enzymes involved in glucose metabolism, prevent the development of insulin resistance, strong antioxidant activity and inhibit the formation of advanced glycation end products, inhibition or expression of several genes which are responsible for diabetes and progression of diabetic complications.

Even several classes of novel natural products are established for the treatment, the utility is less because of untoward effects of drug therapy. So research had done so for on natural products to achieve better treatment than existed therapy with synthetic drugs. As a part of that terpenoids exhibit promising role in the prevention and treatement of diabetes and diabetic complications like retinopathy, nephropathy, neuropathy, embryopathy and other vascular dysfunctions. Table **1** explains the source and involved triterpenes with their mechanism of action how they effect on diabetes and associated complications. Curbitanetriterpenoids are capable of stimulating AMPK activity, favoring GLUT4 translocation, weight loss, and metabolic control

Here we propose that triterpenes as natural multi-target agents, which represent promising therapeutic agents by acting on various molecular mechanisms leading to not only to diabetes but also for diabetic complications. Combinatorial therapy using antidiabetic triterpenoids may also be advantageous. Overall, research on development of triterpenoids in diabetic therapy is in good progress. Safety profile of triterpenoids in toxicity studies represents an advantage for their clinical development. In this context, discovery of antidiabetic new tritepenoids from natural sources as well as a detailed investigations including clinical evaluation on existing antidiabetic tritepenoids are needed for their development as effective and safe drugs for diabetic therapy.

LIST OF ABBREVIATIONS

ABTS	=	2,2'-azino-bis[3-ethylbenzothiazoline-6-sulphonic acid
AGE	=	advanced glycation end products
AMPK	=	5' adenosine monophosphate-activated protein kinase
BSA	=	bovine serum albumin
AT-1	=	angiotensin 1
C/EBP-α	=	CCAAT-enhancer-binding proteins
DGAT	=	Diglyceride acyltransferase
DPPH	=	2,2-diphenyl-1-picrylhydrazyl.
DPP-4	=	dipeptidyl peptidase 4
ERK1/2	=	extracellular signal-regulated protein kinases 1 and 2
GADPH	=	glyceraldehyde-3-Phosphate dehydrogenase
GLP 1	=	Glucagon-like peptide-1
GLUT	=	glucose transporter
HSD1	=	11β-hydroxysteroid dehydrogenase type 1
HSP	=	heat shock protein
iNOS	=	inducible nitric oxide synthase
MDH	=	malate dehydrogenase
NF-kβ	=	nuclear factor kβ
PKB	=	protein kinase B
PKC	=	protein kinase A
PPARγ	=	Peroxisome proliferator-activated receptor gamma
PTB1B	=	protein tyrosine phosphatase 1b_
SDH	=	sorbitol dehydrogenase
SGLT	=	sodium/glucose cotransporter 2
TGF	=	transforming growth factor
TXNIP	=	thioredoxin Interacting Protein

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

G. Aliev thankful to Russian Science Foundation (www.rscf.ru, Российский Научный Фонд, grant number 14-23-00160 for 2014-2016) for financial support for research. Dhananjaya BL (DBL) acknowledge the financial assistance of DST, Govt of India for the International Grant - Indo-Srilankan (DST/INT/SLP/P-007/2012, dated 5th May, 2014), and European Union for International Grant - Indo-European - Marie Curie IRSES - (PIRSES-GA-2013-612131, dated 15th Nov, 2014). Divakar MB and Santosh MS acknowledge the Department of Science and Technology, Govt. of India for the financial support under the Fast Track Young Scientist Scheme. DBL would like to place on record the deepest gratitude towards Dr. Chenraj Roychand, President Jain University trust and Dr. Krishna Venkatesh, CEO, Centre for Emerging Technologies (CET) for their constant motivation and support. Nagendra Sastry Yarla (NSY) expresses his sincere gratitude to GITAM University Management, for his support and encouragement by providing necessary research facilities. NSY is very much thankful to Prof. G. Subrahmanyam and Prof. N. Lakshmana Das for their encouragement and motivation.

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